American Journal of Cardiovascular Drugs
https://doi.org/10.1007/s40256-023-00605-5

REVIEW ARTICLE

The Pivotal Role of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Hypertension Management and Cardiovascular and Renal Protection: A Critical Appraisal and Comparison of International Guidelines

Luis Antonio Alcocer[1] · Alfonso Bryce[2] · David De Padua Brasil[3] · Joffre Lara[4] · Javier Moreno Cortes[5] · Daniel Quesada[6] · Pablo Rodriguez[7]

Accepted: 6 August 2023

Abstract

Arterial hypertension is the main preventable cause of premature mortality worldwide. Across Latin America, hypertension has an estimated prevalence of 25.5–52.5%, although many hypertensive patients remain untreated. Appropriate treatment, started early and continued for the remaining lifespan, significantly reduces the risk of complications and mortality. All international and most regional guidelines emphasize a central role for renin–angiotensin–aldosterone system inhibitors (RAASis) in antihypertensive treatment. The two main RAASi options are angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs). Although equivalent in terms of blood pressure reduction, ACEis are preferably recommended by some guidelines to manage other cardiovascular comorbidities, with ARBs considered as an alternative when ACEis are not tolerated. This review summarizes the differences between ACEis and ARBs and their place in the international guidelines. It provides a critical appraisal of the guidelines based on available evidence from randomized controlled trials (RCTs) and meta-analyses, especially considering that hypertensive patients in daily practice often have other comorbidities. The observed differences in cardiovascular and renal outcomes in RCTs may be attributed to the different mechanisms of action of ACEis and ARBs, including increased bradykinin levels, potentiated bradykinin response, and stimulated nitric oxide production with ACEis. It may therefore be appropriate to consider ACEis and ARBs as different antihypertensive drugs classes within the same RAASi group. Although guideline recommendations only differentiate between ACEis and ARBs in patients with cardiovascular comorbidities, clinical evidence suggests that ACEis provide benefits in many hypertensive patients, as well as those with other cardiovascular conditions.

✉ Pablo Rodriguez
rodripab62@gmail.com; prodriguez@icba.com.ar

1 Instituto Mexicano de Salud Cardiovascular, Mexico City, Mexico

2 Cardiogolf/Clínica El Golf, Lima, Peru

3 Departamento de Medicina, Faculdade de Ciências da Saúde (FCS), Universidade Federal de Lavras (UFLA), Lavras, Minas Gerais, Brazil

4 Hospital Juan Tanca Marengo, Guayaquil, Ecuador

5 Clínica Reina Sofia, Bogota, Colombia

6 Hospital San Vicente de Paúl, Heredia, Costa Rica

7 Instituto Cardiovascular de Buenos Aires, Sanatorio Dr. Julio Méndez, Av del Libertador 6302, C1428ART Buenos Aires, Argentina

Key Points

Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) are the two main classes of renin–angiotensin–aldosterone system inhibitors recommended for hypertension management by international guidelines.

ACEis and ARBs both effectively reduce blood pressure (BP) by different mechanisms of action.

Clinical evidence suggests ACEis provide additional benefits beyond BP control with regard to reducing cardiovascular and mortality risk in patients living with hypertension and other cardiovascular comorbidities.

Published online: 05 September 2023

1 Introduction

Arterial hypertension [i.e., high blood pressure (BP)] is estimated to affect > 1.25 billion people aged 30–79 years worldwide [1]. In addition to being the leading preventable cause of cardiovascular disease (CVD)-related mortality, all-cause mortality, and disease burden, hypertension is one of the main risk factors associated with chronic kidney disease (CKD) and dementia [2]. In 2015, elevated systolic BP (SBP ≥ 115 mmHg) was associated with an estimated 8.5 million deaths worldwide [2]. In Latin American countries, the estimated prevalence of hypertension (BP > 140/90 mmHg) varied among adults aged ≥ 18 years from 25.5% in Mexico to 52.5% in Argentina in 2019, and remained under-treated, with the proportion of untreated individuals with hypertension ranging from 17.4% in Venezuela to 58.3% in Mexico [3].

In addition to lifestyle and dietary modifications, appropriate pharmacologic treatment of hypertension has been shown to significantly reduce hypertension-related complications and increase the quality and duration of life. Clinical evidence has demonstrated that a 5-mmHg reduction in SBP can reduce the risk of stroke or heart failure (HF) by 13% and major adverse cardiovascular event (MACE) by 10%, even in individuals with normal or high–normal BP and regardless of prior CVD diagnoses or risk [4]. Furthermore, intensive antihypertensive treatment (target SBP < 120 or < 130 mmHg) has been shown to further reduce the risk of cardiovascular events, including stroke, acute coronary syndrome (ACS), HF, coronary revascularization, and atrial fibrillation, as well as cardiovascular and all-cause mortality, compared with standard antihypertensive treatment (target SBP < 140 or < 150 mmHg) [5, 6]. However, long-term follow-up (median 8.8 years) suggests that these benefits do not persist after discontinuation of intensive antihypertensive treatment [7]. According to a global impact assessment analysis, an increase in antihypertensive treatment coverage to include 70% of patients with hypertension has the potential to prevent 39 million premature deaths over 25 years, assuming a 15-mmHg decline in SBP [8].

All international and most regional guidelines for the management of hypertension emphasize a central role for renin–angiotensin–aldosterone system inhibitors (RAASis) and recommend their use, either as monotherapy or as combination therapy, as the basis of antihypertensive treatment in most patients, with a preference for single-pill combinations (SPCs) as the first step of treatment [9]. Indeed, a 2021 systematic review found that use of SPCs for antihypertensive therapy was associated with significantly improved rates of adherence and persistence compared with administration of separate equivalent medications [10].

The two main options for RAASis are angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II (Ang II) receptor blockers (ARBs); direct renin inhibitors are rarely used in clinical practice. Although ACEis and ARBs are considered to be equivalent in terms of BP reduction by most hypertension guidelines [9, 11, 12], ACEis are preferably recommended by some cardiovascular guidelines to manage arterial hypertension in patients with different comorbidities [e.g., HF, coronary syndromes, type 2 diabetes (T2D), and CKD], with ARBs considered as an alternative when ACEis are not tolerated [13–21]. Head-to-head randomized controlled trials (RCTs) comparing clinical outcomes with ACEis and ARBs are limited; therefore, meta-analyses are often used to indirectly compare results from different studies of antihypertensive drugs. Of course, results from meta-analyses are considered "hypothesis generating" and should ideally be confirmed in prospective trials. Whereas some meta-analyses have indicated that ARBs and ACEis have similar efficacy with regard to BP-lowering effects and clinical outcomes [22, 23], others suggest that the ACEi drug class is associated with a significantly reduced risk of all-cause mortality and cardiovascular events that is not evident with ARBs [24–27]. A large a meta-analysis of efficacy data from 18 RCTs in hypertension patients (N = 152,886) reported significantly lower hazard ratios (HRs) and numbers needed to treat (NNTs) for all-cause mortality, cardiovascular mortality, and myocardial infarction (MI) in favor of ACEis compared with respective controls, whereas ARBs showed no effect for these outcomes [28].

Hypertension rarely presents in isolation, with hypertensive patients often having other hypertension-related comorbidities, including CKD, diabetes, HF, peripheral artery disease (PAD), atrial fibrillation, or coronary artery disease (CAD) [29]. The presence of these comorbidities often affects the recommended management of hypertension, especially in patients with cardiovascular comorbidities.

The aim of this narrative review is to summarize the differences between ACEis and ARBs and their place in the international hypertension and cardiovascular guidelines. It provides a critical appraisal of the guidelines in accordance with the available evidence from RCTs, especially considering that hypertensive patients in daily clinical practice often have cardiovascular comorbidities.

2 Should the ACEi and ARB Drug Classes be Considered Equivalent?

2.1 Differences in the Mechanisms of Action

Both ACEis and ARBs lower BP through their effects on the Ang II pathway within the RAAS; however, these agents function by acting at different sites in this pathway [30].

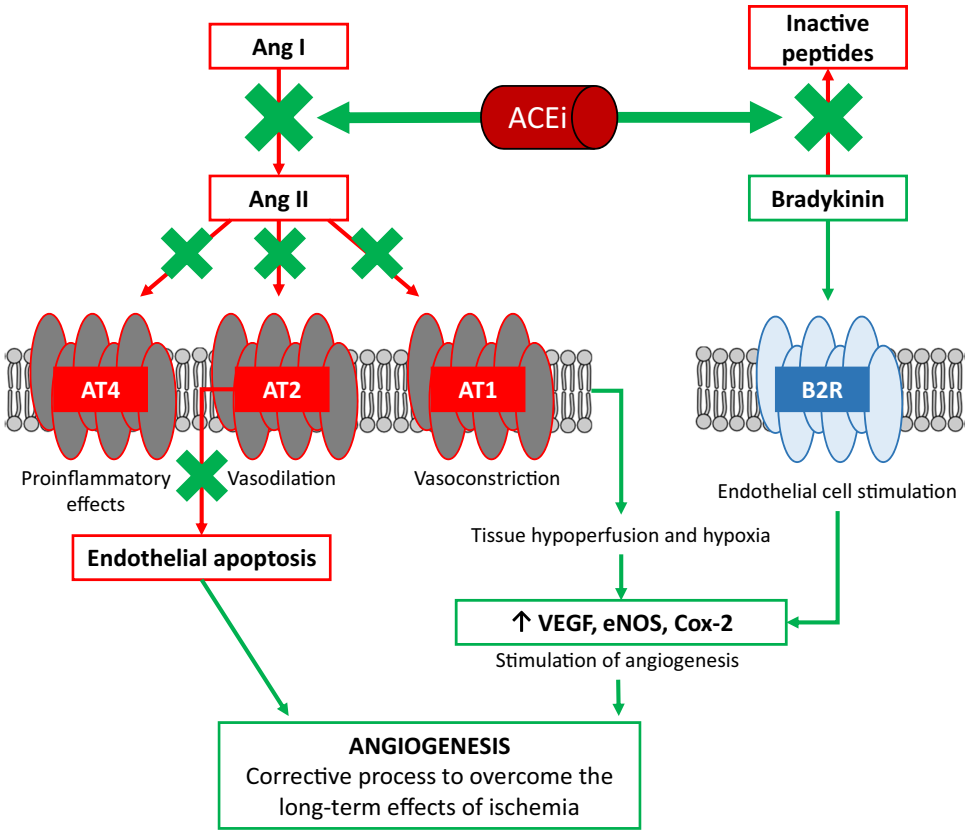

Fig. 1 Mechanism of action for angiotensin-converting enzyme inhibitors (ACEis). ACEis block the conversion of angiotensin I to angiotensin II, thereby blocking its action on multiple different receptors (AT1, AT2, and AT4) involved in vasodilation, vasoconstriction, apoptosis, inflammation, and angiogenesis. ACEi therapy is also associated with an increase in bradykinin levels and bradykinin-mediated stimulation of angiogenesis, which can lead to improved hypoxia-induced neovascularization. *ACEi* angiotensin-converting enzyme inhibitor, *Ang* angiotensin, *Cox-2* cyclooxygenase-2, *eNOS* endothelial nitric oxide synthase, *VEGFR* vascular endothelial growth factor receptor

Ang II is a peptide hormone that is responsible for regulation of systemic arterial pressure by causing vasoconstriction, modulation of the sympathetic nervous system, and retention of sodium and water by the kidneys [31]. ACEis prevent the conversion of Ang I to Ang II, thereby reducing the availability of Ang II to act on Ang II type 1 (AT1) and type 2 (AT2) receptors and lowering BP (Fig. 1) [32]. ACEis also prevent ACE-mediated degradation of bradykinin, thus causing an increase in plasma bradykinin levels and increased endothelial nitric oxide production [30]. The increase in bradykinin levels with ACEis stimulates vasodilation, vascular permeability, and prostaglandin production [30], and contributes to restoration of fibrinolytic balance, improved endothelial function, and enhanced ischemic conditioning [33]. ACEis may also potentiate the bradykinin response by inhibiting the desensitization of bradykinin 2 receptors, which are constitutively expressed in most tissues and are responsible for mediating the vasodilatory effects of the bradykinin response [30]. In patients with cardiovascular risk factors or CAD, tissue overexpression of ACE disturbs the balance of bradykinin and Ang II (i.e., decreased bradykinin levels and increased Ang II levels), which causes endothelial dysfunction [34]. The duration of action for ACEis varies within the drug class, with the effective half-life ranging from 1 to 2 h for short-acting agents (e.g., captopril, quinapril, and perindopril) to 10–12 h for longer-acting agents (e.g., enalapril and lisinopril) [35].

In contrast with ACEis, ARBs selectively block the binding of Ang II to AT1 receptors (Fig. 2) [36, 37], which are found in the heart, blood vessels, kidneys, adrenal glands, and circumventricular organs of the brain [38]. In addition to blocking AT1 receptors, ARBs can simultaneously stimulate AT2 receptors [37], which is thought to reduce BP-induced vascular remodeling by inhibiting perivascular fibrosis, coronary artery thickening, and vascular injury inflammation [39]. Further to these cardiovascular benefits, ARBs have been associated with protective effects in the kidneys (attributed to blockade of renal RAAS) and brain (due to reduction in middle cerebral artery thickness and smaller decreases in cerebral blood flow during ischemia) [37, 40, 41]. Many ARBs have a longer duration of action than ACEis, with an effective half-life of 13 h for olmesartan, 11–15 h for irbesartan, and 24 h for telmisartan [35].

Despite having different mechanisms of action, both ACEis and ARBs are associated with anti-inflammatory effects and decreased oxidative stress [42]. Data from animal studies suggest that ACEis may upregulate endothelial progenitor cells from the bone marrow, thereby enhancing extracardiac neoangiogenesis during cardiac remodeling [43]. In patients with CAD, treatment with the ACEi perindopril

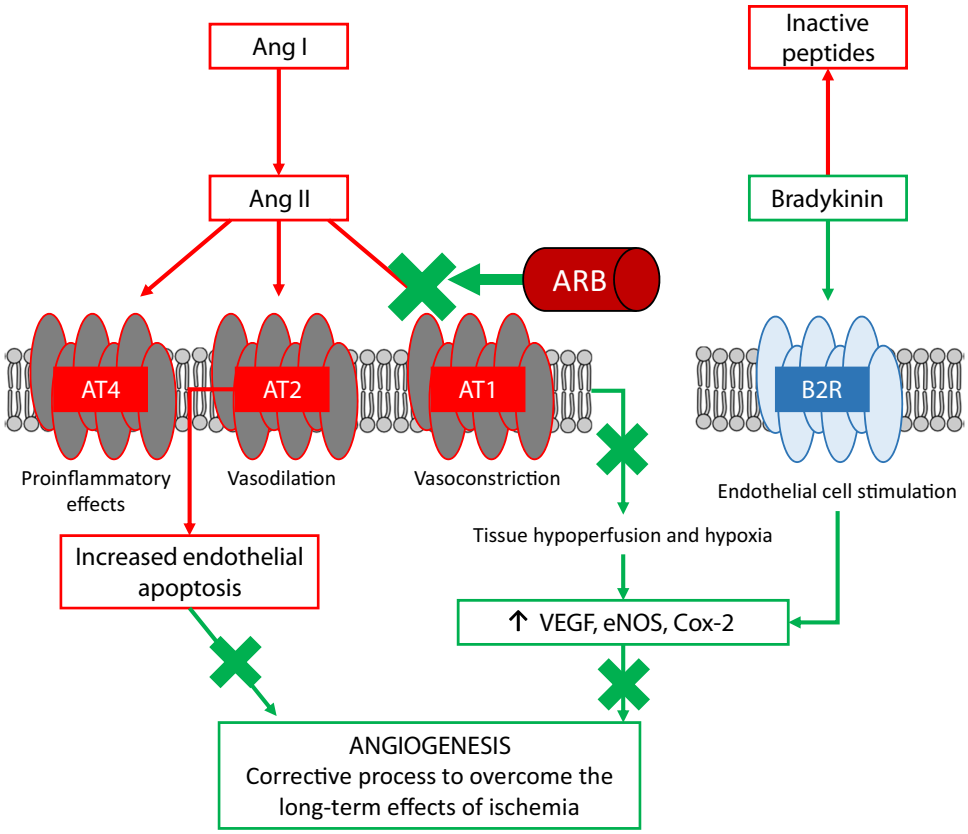

Fig. 2 Mechanism of action for angiotensin receptor blockers (ARBs). ARBs inhibit the binding of angiotensin II to the AT1 receptor, thereby preventing vasoconstriction. However, the increased angiotensin II levels can lead to stimulation of AT2 and AT4 receptors, which can cause inappropriate endothelial apoptosis and release of proinflammatory cytokines. Long-term ARB therapy may also play a role in microvascular rarefaction, cardiac remodeling (including left ventricular hypertrophy), and fibrosis. *Ang*, angiotensin, *ARB* angiotensin receptor blocker, *Cox-2* cyclooxygenase-2, *eNOS* endothelial nitric oxide synthase, *VEGFR* vascular endothelial growth factor receptor

was also shown to upregulate endothelial nitric oxide synthase expression and activity [44].

ARBs have been shown to have anti-inflammatory effects in animal models, largely mediated by blocking AT1 receptors, including inhibiting the release of pro-inflammatory cytokines [i.e., tumor necrosis factor (TNF)-α and interleukin (IL)-6] and aldosterone, preserving glucocorticoid release, and suppressing the expression of pro-inflammatory genes and cerebral microglial activation [45, 46]. Data from a 2022 meta-analysis of 32 RCTs ($N = 3489$ patients) indicated that ACEis provided significant reductions in C-reactive protein (CRP; $I^2 = 99\%$), IL-6 ($I^2 = 0\%$), and TNF-α ($I^2 = 99\%$) levels, and ARBs provided significant reductions in IL-6 levels ($I^2 = 85\%$), but did not significantly affect the other two inflammatory markers ($I^2 = 0\%$ and 77%, respectively) [47].

Long-term ARB treatment does not upregulate bradykinin but can lead to compensatory increases in plasma Ang II levels [33, 48]. Elevated Ang II levels may stimulate the Ang III–IV pathways, which results in overactivation of the AT2 and AT4 receptors [30]. Together with TNF-α, Ang II has been associated with cardiac remodeling, left ventricular hypertrophy, and increased vascular fibrosis in an animal model by increasing oxidative stress [49]. AT1 receptor activation in response to Ang II is also thought to stimulate acute release of plasminogen activator inhibitor-I [50], which is associated with development of CAD and an independent predictor of mortality in patients with ST-segment elevation MI (STEMI) [51]. Through its interaction with AT2 receptors, Ang II also has a central role in mediating prostaglandin E2-dependent macrophage production of matrix metalloproteinases, which are associated with atherosclerotic plaque rupture [52]. Ang IV-induced activation of AT4 receptors may lead to inflammation in vascular smooth muscle cells through the upregulation of the nuclear factor-κB pathway and expression of other proinflammatory factors [53]. However, Ang IV binding to AT4 receptors may also counteract Ang II-mediated cardiac cell apoptosis, cardiomyocyte hypertrophy, and fibroblast proliferation [54].

2.2 Clinical Evidence for ACEi and ARB Efficacy in Different Clinical Scenarios

In patients with hypertension, there is clinical evidence that both ACEis and ARBs have similar efficacy with regard to lowering BP [55]. However, there is also placebo-controlled evidence that ACEis provide significant reductions in the risk of cardiovascular morbidity and mortality in several different study populations, in which the proportion of patients with hypertension ranged from 7 to 100% (Table 1). Three prospective trials have directly compared the effects of ACEis versus ARBs on clinical outcomes in patients with

cardiovascular disease (i.e., ONTARGET, OPTIMAAL, and VALIANT).

2.2.1 Elderly Patients

In the HYVET study in very elderly patients with persistent hypertension, treatment with the thiazide-like diuretic indapamide, with or without the ACEi perindopril, was associated with a significant reduction in the risk of death from stroke ($p = 0.046$), death from any cause ($p = 0.02$), HF ($p < 0.001$), and any cardiovascular event ($p < 0.001$) compared with placebo [56]. Of note, almost three-quarters of patients in the active-treatment group (73.4%) were receiving both indapamide and perindopril, with only 25.8% receiving indapamide alone.

The SCOPE study in elderly hypertensive patients demonstrated a significant reduction in the risk of nonfatal stroke with the ARB candesartan compared with placebo ($p = 0.04$), but candesartan provided only a modest, nonsignificant reduction in the risk of MACE ($p = 0.19$) [57]. There was no significant difference in the risk of cardiovascular or all-cause mortality compared with placebo. In this study, 26% of patients in the candesartan group were receiving low-dose (12.5 mg) hydrochlorothiazide from randomization, while 49% started other open-label add-on antihypertensive treatment during the study [including hydrochlorothiazide at an increased dose or started after randomization, a β-blocker, or calcium channel blocker (CCB)].

2.2.2 High Cardiovascular Risk

In the HOPE study in patients with evidence of CVD or diabetes plus another cardiovascular risk factor, the ACEi ramipril significantly reduced the risk of the composite outcome of cardiovascular mortality, MI, or stroke ($p < 0.001$) and death from any cause ($p = 0.005$) compared with placebo [58]. Similarly, perindopril in combination with amlodipine was associated with significant reductions in the risks of cardiovascular mortality ($p = 0.0010$), all-cause mortality ($p = 0.0247$), and all cardiovascular events ($p < 0.0001$) compared with atenolol plus a thiazide diuretic among hypertensive patients with three or more other cardiovascular risk factors in the ASCOT-BPLA study [59].

The placebo-controlled TRANSCEND study in patients with CVD or high-risk diabetes who were intolerant to ACEis demonstrated a modest, albeit significant, reduction in the risk of MACE with the ARB telmisartan compared with placebo ($p = 0.048$); however, there was no significant effect on cardiovascular mortality, all-cause mortality, or MACE plus hospitalization for HF [60]. The ARB valsartan also had noninferior efficacy to amlodipine for the composite outcome of cardiovascular morbidity and mortality among hypertensive patients with high cardiovascular risk in the VALUE study ($p = 0.49$) [61], and showed no difference in the extended composite cardiovascular outcome (cardiovascular mortality, nonfatal MI, nonfatal stroke, hospitalization for HF, arterial revascularization or hospitalization for unstable angina) compared with placebo in patients with impaired glucose tolerance and one or more cardiovascular risk factors or established CVD in the NAVIGATOR study ($p = 0.85$) [62]. Of note, the risk of MI was significantly increased with valsartan versus amlodipine in VALUE ($p = 0.02$) [61].

The ONTARGET study in patients with CVD or high-risk diabetes compared cardiovascular outcomes with an ARB (telmisartan) versus an ACEi (ramipril) [63]. This study found that the cardioprotective effects of telmisartan were noninferior to those of ramipril after 56 months of follow-up, with no difference in the risk of the composite cardiovascular outcome of cardiovascular mortality, MI, stroke, or hospitalization for HF ($p = 0.004$ for noninferiority). The risk of MI was 7% higher with telmisartan versus ramipril, although this difference was not statistically significant [63]. Based on these results, as well as data from the TRANSCEND study [60], telmisartan was approved by the US Food and Drug Administration (FDA) for cardiovascular risk reduction in patients who are unable to receive ACEis [64].

In a meta-analysis of 26 RCTs in 108,212 high cardiovascular-risk patients without HF, the risk of the composite outcome of cardiovascular death, MI, or stroke was significantly reduced with ACEis [odds ratio (OR) 0.830, 95% confidence interval (CI) 0.744–0.927; $p = 0.001$; $I^2 = 62.1\%$] and ARBs (OR 0.920, 95% CI 0.869–0.975; $p = 0.005$; $I^2 = 0.0\%$) [25]. ACEis also significantly reduced the risk of all-cause death (OR 0.908, 95% CI 0.845–0.975; $p = 0.008$; $I^2 = 7.8\%$), MI (OR 0.811, 95%CI 0.748–0.879; $I^2 = 0.6\%$), and new-onset HF (OR 0.789, 95% CI 0.686–0.908; $I^2 = 21.5\%$), whereas there was no significant effect on these risks with ARBs (all-cause death OR 1.006, 95% CI 0.941–1.075; $p = 0.866$; $I^2 = 0.0\%$; MI OR 0.903, 95% CI 0.803–1.015; $p = 0.086$; $I^2 = 2.1\%$; and new-onset HF OR 0.892, 95% CI 0.761–1.046; $p = 0.159$; $I^2 = 31.4\%$) [25].

2.2.3 Coronary Syndromes

In patients with stable CAD in the EUROPA study, the ACEi perindopril was associated with a 20% reduction in the relative risk of the primary endpoint (i.e., composite outcome of cardiovascular mortality, MI, or cardiac arrest with successful resuscitation) compared with placebo ($p = 0.0003$); however, the reduction in the relative risks of cardiovascular mortality or all-cause mortality did not reach statistical significance [65]. In EUROPA, only 27% of patients had hypertension at baseline; nevertheless, a prespecified subgroup analysis showed that the beneficial effects of perindopril with regard to the primary endpoint were observed in

Table 1 Summary of clinical evidence for the reduction in the cardiovascular risk with ACEis and ARBs in different patient populations

Study	Patient population	HTN (%)	Treatment (follow-up)	Main outcomes
Elderly patients				
HYVET [56]	Aged ≥ 80 years (n = 3845)	100	Thiazide-like diuretic (indapamide) ± ACEi (perindopril) vs placebo (median 1.8 years)	All-cause mortality: HR 0.79, 95% CI 0.65–0.95; p = 0.02 CV mortality: HR 0.77, 95% CI 0.60–1.01; p = 0.06 Death from stroke: HR 0.61, 95% CI 0.38–0.99; p = 0.046 Any CV event: HR 0.66, 95% CI 0.53–0.82; p < 0.001 Any HF event: HR 0.36, 95% CI 0.22–0.58; p < 0.001
SCOPE [57]	Aged 70–89 years (n = 4964)	100	ARB (candesartan) vs placebo (mean 3.7 years)	All-cause mortality; no significant difference CV mortality; no significant difference MACE (CV mortality, nonfatal MI, or stroke): RR 0.89, 95% CI 0.75–1.06; p = 0.19 Nonfatal stroke: RR 0.72, 95% CI 0.53–0.99; p = 0.04 All stroke: RR 0.76, 95% CI 0.58–1.07; p = 0.056
Patients with high CV risk				
HOPE [58]	Aged ≥ 55 years with high CV risk (n = 9297)	47	ACEi (ramipril) versus placebo (mean 5 years)	MACE (CV death, MI, or stroke): RR 0.78, 95% CI 0.70–0.86; p < 0.001 All-cause mortality: RR 0.84, 95% CI 0.75–0.95; p = 0.005 CV mortality: RR 1.03, 95% CI 0.85–1.26; p = 0.74
ASCOT-BPLA [59]	Aged 40–79 years with ≥ 3 CV risk factors (n = 19,257)	100	ACEi (perindopril) + amlodipine versus atenolol + bendroflumethiazide (median 5.5 years)	Total CV events/procedures: HR 0.84, 95% CI 0.78–0.90; p < 0.0001 All-cause mortality: HR 0.89, 95% CI 0.81–0.99; p = 0.0247 CV mortality: HR 0.76, 95% CI 0.65–0.90; p = 0.0010
TRANSCEND [60]	Aged ≥ 55 years with CVD or T2D with end-organ damage and ACEi intolerance (n = 5926)	76	ARB (telmisartan) versus placebo (median 56 months)	CV death, MI, stroke, or HHF: HR 0.92, 95% CI 0.81–1.05; p = 0.216 MACE (CV death, MI, or stroke): HR 0.87, 95% CI 0.76–1.00; p = 0.048 All-cause mortality: HR 1.05, 95% CI 0.91-1.22; p = 0.491 CV mortality: HR 1.03, 95% CI 0.85–1.24; p = 0.778
VALUE [61]	Aged ≥ 50 years with CV risk factors or CVD (n = 15,313)	100	ARB (valsartan) versus amlodipine (mean 4.2 years)	All-cause mortality: HR 1.04, 95% CI 0.94–1.14; p = 0.45 CV morbidity and mortality: HR 1.03, 95% CI 0.94–1.14; p = 0.49 MI: HR 1.19, 95% CI 1.02–1.38; p = 0.02
NAVIGATOR [62]	Aged ≥ 55 years with impaired glucose tolerance and ≥ 1 CV risk factor or aged ≥ 50 years with established CVD (n = 9518)	78	ARB (valsartan) versus placebo (median 5.0 years)	All-cause mortality: HR 0.90, 95% CI 0.77–1.05; p = 0.17 CV mortality: HR 1.09, 95% CI 0.85–1.40; p = 0.52 Extended composite CV outcome[a]: HR 0.99, 95% CI 0.86–1.14; p = 0.85 CV death, MI, stroke, or HHF: HR 0.99, 95% CI 0.86–1.14; p = 0.85
ONTARGET [63]	**Aged ≥ 55 years with CVD or T2D with end-organ damage (n = 25,620)**	**69**	**ARB (telmisartan) versus ACEi (ramipril) (median 56 months)**	**CV mortality, MI, stroke, or HHF: HR 1.01, 95% CI 0.94–1.09; p = 0.004 for noninferiority** **CV mortality, MI, or stroke: HR 0.99, 95% CI 0.91–1.07** **MI: HR 1.07, 95% CI 0.94–1.22**

Table 1 (continued)

Study	Patient population	HTN (%)	Treatment (follow-up)	Main outcomes
Patients with CAD				
EUROPA [65]	Aged ≥ 18 years with CAD (n = 13,655)	27	ACEi (perindopril) versus placebo (mean 4.2 years)	All-cause mortality: RR 0.89, 95% CI 0.77–1.02); $p = 0.1$ CV mortality: RR 0.86, 95% CI 0.72–1.03; $p = 0.107$ CV mortality, MI, or cardiac arrest: RR 0.80, 95% CI 0.71–0.91; $p = 0.0003$
PEACE [66]	Aged ≥50 years with CAD and preserved LV function (n = 8290)	46	ACEi (trandolapril) versus placebo (median 4.8 years)	All-cause mortality: HR 0.89, 95% CI 0.76–1.04; $p = 0.13$ CV mortality: HR 0.95, 95% CI 0.76–1.19; $p = 0.67$ CV mortality, nonfatal MI, CABG, or PCI: HR 0.96, 95% CI 0.88–1.06; $p = 0.43$
QUIET [67]	Aged 18–75 years with CAD and preserved LV function (n = 1750)	47	ACEi (quinapril) versus placebo (median 27 months)	Ischemic events: RR 1.04, 95% CI 0.89–1.22; $p = 0.6$ Angioplasty for previous nonintervened vessels: $n = 79$ (quinapril) versus 114 (placebo); $p = 0.018$ Angiographic progression of CAD: 47% (quinapril) versus 49% (placebo); $p = 0.71$
Patients with acute MI				
SAVE [68]	Aged 21–80 years with MI with LVEF ≤ 40% (n = 2231)	43	ACEi (captopril) versus placebo (mean 42 months)	All-cause mortality: HR 0.81, 95% CI 0.68–0.97; $p = 0.019$ CV mortality: HR 0.79, 95% CI 0.65–0.95; $p = 0.014$ Severe HF: HR 0.67, 95% CI 0.50–0.80; $p < 0.001$ Hospitalization for CHF: HR 0.78, 95% CI 0.63–0.96; $p = 0.019$ Recurrent MI: HR 0.75, 95% CI 0.60–0.95; $p = 0.015$
CONSENSUS II [72]	Aged ≥ 18 years with acute MI (n = 6090)	NR	ACEi (enalapril) versus placebo (41–180 days)	All-cause mortality: HR 1.10, 95% CI 0.93–1.29; $p = 0.26$ Death due to progressive HF: 4.3% (enalapril) versus 3.4% (placebo); $p = 0.06$
AIRE [69]	Aged ≥ 18 years with acute MI and HF (n = 2006)	28	ACEi (ramipril) versus placebo (mean 15 months)	All-cause mortality: HR 0.73, 95% CI 0.60–0.89; $p = 0.002$ Death, reinfarction, stroke, or severe/resistant HF: HR 0.81, 95% CI 0.69–0.95; $p = 0.008$
TRACE [70]	Aged ≥ 18 years with recent acute MI (n = 1749)	23	ACEi (trandolapril) versus placebo (24–50 months)	All-cause mortality: RR 0.78, 95% CI 0.67–0.91; $p = 0.001$ CV mortality: RR 0.75, 95% CI 0.63–0.89; $p = 0.001$ Sudden death: RR 0.76, 95% CI 0.59–0.98; $p = 0.03$ Progression to severe HF: RR 0.71, 95% CI 0.56–0.89; $p = 0.003$ Recurrent MI: RR 0.86, 95% CI 0.66–1.13; $p = 0.29$
SMILE [71]	Aged 18–80 years with recent MI (n = 1556)	40	ACEi (zofenopril) versus placebo (1 year)	All-cause mortality (1 year): HR 0.71, 95% CI 0.49–0.94; $p = 0.011$ Death or severe CHF (6 weeks): HR 0.66, 95% CI 0.46–0.92; $p = 0.018$
OPTIMAAL [73]	**Aged ≥ 50 years with acute MI and HF (n = 5477)**	**36**	**ARB (losartan) versus ACEi (captopril) (mean 2.7 years)**	**All-cause mortality: RR 1.13, 95% CI 0.99–1.28; $p = 0.69$** **MI mortality: RR 1.10, 95% CI 0.99–1.22; $p = 0.085$** **CV mortality: RR 1.17, 95% CI 1.01–1.34; $p = 0.032$**
VALIANT [74]	**Aged ≥ 18 years with acute MI and HF, LV dysfunction, or both (n = 14,703)**	**55**	**ARB (valsartan) versus ACEi (captopril) (median 24.7 months)**	**All-cause mortality: HR 1.00, 95% CI 0.90–1.11; $p = 0.004$ for non-inferiority; $p = 0.98$ for superiority** **CV mortality: HR 0.98, 95% CI 0.87–1.09; $p = 0.62$**

Table 1 (continued)

Study	Patient population	HTN (%)	Treatment (follow-up)	Main outcomes
Patients with HF				
CONSENSUS [75]	Severe CHF ($n = 253$)	22	ACEi (enalapril) versus placebo (mean 188 days)	All-cause mortality (6 months): 40% reduction; $p = 0.002$ All-cause mortality (12 months): 31% reduction; $p = 0.001$ All-cause mortality (end of study): 27% reduction; $p = 0.003$ Any cardiac death: $p = 0.001$ Death due to congestive HF: 50% reduction; $p = 0.001$
SOLVD [76]	Aged < 80 years with HF with EF ≤ 35%	42	ACEi (enalapril) versus placebo (mean 41.4 months)	All-cause mortality: HR 0.84, 95% CI 0.74–0.95; $p = 0.0036$ Death or hospitalization for HF: HR 0.74, 95% CI 0.66–0.82; $p < 0.0001$
CHARM-Alternative [77]	Aged ≥ 18 years with HF with LVEF ≤ 40% with ACEi intolerance ($n = 2028$)	50	ARB (candesartan) versus placebo (median 33.7 months)	All-cause mortality: HR 0.83, 95% CI 0.70–0.99; $p = 0.033$ CV death or hospitalization for CHF: adjusted HR 0.70, 95% CI 0.60–0.81; $p < 0.0001$ CV death: adjusted HR 0.80, 95% CI 0.66–0.97; $p = 0.02$ Hospitalization for CHF: adjusted HR 0.61, 95% CI 0.51–0.73; $p < 0.0001$ MI: HR 1.52, 95% CI 1.06–2.18; $p = 0.025$
Val-HeFT [78]	Aged ≥18 years with HF with LVEF < 40% ($n = 5010$)	7	ARB (valsartan) versus placebo (mean 23 months)	All-cause mortality: RR 1.02, 95% CI 0.88–1.18; $p = 0.80$ Morbidity and mortality[b]: RR 0.87, 95% CI 0.77–0.97; $p = 0.009$
Patients with prior stroke				
PROGRESS [81]	Prior stroke or TIA ($n = 6105$)	48	ACEi (perindopril) + indapamide versus placebo (mean 3.9 years)	All-cause mortality: RR 0.96, 95% CI 0.82–1.12 Recurrent stroke: RR 0.72, 95% CI 0.62–0.83; $p < 0.0001$ Non-fatal stroke: RR 0.71, 95% CI 0.61–0.83 CV death: RR 0.91, 95% CI 0.75–1.12 Non-fatal MI: RR 0.62, 95% CI 0.45–0.86
PROFESS [82]	Aged ≥ 55 years with recent ischemic stroke ($n = 20,332$)	74	ARB (telmisartan) versus placebo (mean 2.5 years)	Recurrent stroke: HR 0.95, 95% CI 0.86–1.04; $p = 0.23$ Major CV event[c]: HR 0.94, 95% CI 0.87–1.01; $p = 0.11$
Patients with T2D				
ADVANCE [83]	Aged ≥ 55 years with T2D and major CVD or ≥ 1 CV risk factor ($n = 11,140$)	69	ACEi (perindopril) + indapamide versus placebo (mean 4.3 years)	All-cause mortality: RR 0.86, 95% CI 0.75–0.98; $p = 0.025$ CV mortality: RR 0.82, 95% CI 0.68–0.98; $p = 0.027$ Total coronary events: RR 0.86, 95% CI 0.76–0.98; $p = 0.020$ Total renal events: RR 0.79, 95% CI 0.73–0.85; $p < 0.0001$
RENAAL [86]	Aged 31–70 years with T2D and nephropathy ($n = 1513$)	93	ARB (losartan) versus placebo (mean 3.4 years)	All-cause mortality: HR 1.02, 95% CI 0.71–1.27; $p = 0.88$ Doubling of serum creatinine, ESRD, or death: HR 0.84, 95% CI 0.72–0.98; $p = 0.02$ ESRD: HR 0.72, 95% CI 0.58–0.89; $p = 0.002$ CV morbidity or mortality[d]: HR 0.90; $p = 0.26$ HHF: HR 0.68; $p = 0.005$

Table 1 (continued)

Study	Patient population	HTN (%)	Treatment (follow-up)	Main outcomes
IDNT [87]	Aged 30–70 years with T2D and nephropathy ($n = 1715$)	100	ARB (irbesartan) versus placebo (mean 2.6 years)	All-cause mortality: adjusted RR 0.94, 95% CI 0.70–1.27; $p = 0.69$ Composite CV outcome[e]: adjusted RR 0.91, 95% CI 0.72–1.14; $p = 0.40$ Doubling of sCR, ESRD, or death: adjusted RR 0.81, 95% CI 0.67–0.99; $p = 0.03$ Doubling of sCR: adjusted RR 0.71, 95% CI 0.54–0.92; $p = 0.009$ ESRD: adjusted RR 0.83, 95% CI 0.62–1.11; $p = 0.19$
IRMA-2 [88]	Aged 30–70 years with T2D and microalbuminuria ($n = 590$)	100	ARB (irbesartan) versus placebo (median 2 years)	Nonfatal CV events: 4.5% (irbesartan) versus 8.7% (placebo); $p = 0.11$ Diabetic nephropathy: adjusted HR 0.32, 95% CI 0.15–0.65; $p < 0.001$
ORIENT [89]	Aged 30–70 years with T2D ($n = 577$)	92	ARB (olmesartan) versus placebo (mean 3.4 years)	All-cause mortality: aHR 0.99, 95% CI 0.53–1.86 Composite CV outcome[f]: aHR 0.64, 95% CI 0.43–0.98; $p = 0.039$ CV mortality: aHR 2.81, 95% CI 0.76–10.38 Doubling of sCR, ESRD, or death: aHR 0.97, 95% CI 0.75–1.24; $p = 0.791$ Doubling of sCR: aHR 0.94, 95% CI 0.73–1.23 ESRD: aHR 1.08, 95% CI 0.78–1.49
ROADMAP [90]	Aged 18–75 years with T2D + ≥ 1 CV risk factor ($n = 4449$)	NR	ARB (olmesartan) versus placebo (median 3.2 years)	All-cause mortality: HR 1.70, 95% CI 0.90–3.22; $p = 0.10$ CV mortality: HR 4.94, 95% CI 1.43–17.06; $p = 0.01$ All CV complications: HR 0.87, 95% CI 0.65–1.18; $p = 0.37$

Three trials that directly compared ACEis versus ARBS are presented in bold

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *aHR* adjusted hazard ratio, *CAD* coronary artery disease, *CHF* congestive heart failure, *CI* confidence interval, *CV* cardiovascular, *CVD* cardiovascular disease, *EF* ejection fraction, *ESRD* end-stage renal disease, *HF* heart failure, *HHF* hospitalization for heart failure, *HR* hazard ratio, *HTN* hypertension, *HUA* hospitalization for unstable angina, *LV* left ventricular, *MI* myocardial infarction, *NR* not reported, *RR* relative risk, *sCR* serum creatinine, *T2D* type 2 diabetes, *TIA* transient ischemic attack

[a]The composite outcome of CV death, nonfatal MI, nonfatal stroke, HHF, arterial revascularization, or HUA

[b]The composite outcome of cardiac arrest with resuscitation, HHF, or administration of intravenous inotropic or vasodilatory therapy for ≥ 4 h without hospitalization

[c]The composite outcome of CV death, recurrent stroke, MI, or new or worsening HF

[d]The composite outcome of MI, stroke, HHF, HUA, coronary or peripheral revascularization, or CV death

[e]The composite outcome of CV death, non-fatal MI, HHF, a cerebrovascular event resulting in permanent neurologic deficit, or an above the ankle lower limb amputation

[f]The composite outcome of CV death, nonfatal stroke (except for TIA), nonfatal MI, HUA, HHF, arterial revascularization, or lower extremity amputation

patients with or without hypertension [65], providing strong support for the use of perindopril in all patients with stable CAD, regardless of whether or not they are hypertensive. In contrast, the PEACE study in patients with stable CAD and preserved left ventricular (LV) function found that the ACEi trandolapril did not significantly reduce the risk of all-cause mortality ($p = 0.13$), cardiovascular mortality ($p = 0.67$), or the composite outcome of cardiovascular mortality, nonfatal MI, or coronary revascularization ($p = 0.43$) [66]. In the QUIET study of patients with angiographic evidence of CAD but without systolic LV dysfunction, the ACEi quinapril was associated with a significant reduction in the incidence of angioplasty for previously nonintervened vessels compared with placebo ($p = 0.018$), but did not significantly reduce the relative risk of ischemic events ($p = 0.6$) or the incidence of angiographic CAD progression ($p = 0.71$) [67].

Of note, in a systematic review of eight RCTs in 37,148 patients with ischemic heart disease (IHD), ACEis were associated with a reduced risk of total mortality [relative risk (RR) 0.87, 95% CI 0.81–0.94] and cardiovascular mortality (RR 0.83, 95% CI 0.70–0.98) compared with placebo, whereas these risks were not reduced with ARBs [24].

Early studies showed the cardiovascular benefits of ACEis in patients with recent MI [68–71]. In the SAVE study in patients with MI and LV dysfunction, the ACEi captopril significantly reduced the risk of death from any cause ($p = 0.019$), cardiovascular mortality ($p = 0.014$), and recurrent MI ($p = 0.015$) compared with placebo [68]. Similarly, among patients with acute MI and clinical evidence of HF in the AIRE study, ramipril provided significant reductions in the risks of all-cause mortality ($p = 0.002$) and the composite outcome of death, reinfarction, stroke, or severe/resistant HF ($p = 0.008$) compared with placebo [69]. The TRACE study in patients with recent MI reported a significantly reduced risk of all-cause mortality ($p = 0.001$), cardiovascular mortality ($p = 0.001$), and sudden death ($p = 0.03$) with trandolapril versus placebo, although the risk of recurrent MI was not significantly reduced [70]. Similarly, zofenopril was associated with a significant reduction in the risk of all-cause mortality after 1 year compared with placebo ($p = 0.011$) in patients with recent acute MI in the SMILE study [71]. In contrast, the CONSENSUS II study in patients with acute MI reported no significant reduction in the risk of mortality with enalapril versus placebo ($p = 0.26$) and a trend towards a higher incidence of death due to progressive HF in the enalapril group [72].

Two studies have compared ARBs with the ACEi captopril in patients with acute MI [73, 74]. In the OPTIMAAL study in patients with acute MI and HF, there was no significant difference in the risk of all-cause mortality between the ARB losartan and captopril; however, the relative risk of cardiovascular death was lower with captopril versus losartan ($p = 0.032$) [73]. The VALIANT study in patients with acute MI complicated by HF, LV dysfunction, or both found that valsartan was noninferior to captopril with regard to all-cause ($p = 0.98$) or cardiovascular ($p = 0.62$) mortality compared with captopril [74].

2.2.4 Heart Failure

Early studies of the ACEi enalapril in patients with severe congestive HF (CONSENSUS) or congestive HF with reduced ejection fraction (HFrEF; SOLVD) demonstrated a significant reduction in the risk of all-cause mortality compared with placebo [75, 76]. In CONSENSUS, the reduced risk of mortality was largely driven by a significant reduction in the risk of death caused by progressive HF with enalapril versus placebo ($p < 0.001$) [75]. In SOLVD, enalapril was also associated with a reduced risk of hospitalization for HF compared with placebo ($p < 0.0001$) [76].

In the CHARM-Alternative study in patients with HFrEF with intolerance to ACEis, the ARB candesartan significantly reduced the risks of cardiovascular mortality ($p = 0.02$), all-cause mortality ($p = 0.033$), and the composite outcome of cardiovascular death or hospitalization for congestive HF ($p < 0.0001$) [77]. However, in the Val-HeFT study in patients with HFrEF, valsartan, in addition to usual therapy (including ACEi), did not significantly reduce the all-cause mortality risk compared with placebo ($p = 0.80$), although the risk of the combined morbidity and mortality outcome was reduced ($p = 0.009$) [78].

In a meta-analysis of 17 RCTs in 12,469 patients with symptomatic HF, ARBs showed a nonsignificant trend toward reducing the risk of mortality (OR 0.68, 95% CI 0.38–1.22) and hospitalization (OR 0.67, 95% CI 0.80–1.13) compared with placebo [79]. However, when compared with ACEis, ARBs showed no difference in the risk of mortality (OR 1.09, 95% CI 0.92–1.29) or hospitalization (OR 0.95, 95% CI 0.80–1.13) [79]. A more recent meta-analysis of 38 RCTs in a total of 47,662 patients with HF found that ACEis reduced the risk of death from any cause (RR 0.82, 95% CI 0.76–0.89; $p < 0.00001$; $I^2 = 13\%$) and from cardiovascular causes (RR 0.81, 95% CI 0.73–0.89; $p < 0.0001$; $I^2 = 51\%$) compared with placebo; however, the all-cause and cardiovascular mortality risk was not significantly reduced with ARBs versus placebo (RR 0.98, 95% CI 0.90–1.07; $p = 0.28$; $I^2 = 0\%$ and 1.01, 95% CI 0.92–1.12; $p = 0.78$; $I^2 = 40\%$, respectively) [80].

2.2.5 Stroke

In patients with prior stroke or transient ischemic attack (TIA), indapamide plus the ACEi perindopril significantly reduced the relative risk of recurrent stroke, nonfatal stroke, and nonfatal MI compared with placebo in the PROGRESS study, but the risks of cardiovascular mortality and all-cause

mortality were not reduced [81]. In this study, indapamide plus perindopril provided a reduction in the risk of recurrent stroke by 32% in hypertensive patients and 27% in nonhypertensive patients, and a reduction in the risk of major vascular events by 29% and 24%, respectively [81]. In contrast, the ARB telmisartan did not significantly reduce the risk of recurrent stroke ($p = 0.23$) or major cardiovascular events ($p = 0.11$) compared with placebo among patients with recent ischemic stroke in the PROFESS study [82].

2.2.6 Type 2 Diabetes

The ADVANCE study in patients with T2D and nephropathy demonstrated that indapamide plus the ACEi perindopril significantly reduced the relative risk of death from any cause ($p = 0.025$), cardiovascular mortality ($p = 0.027$), total coronary events ($p = 0.020$), and total renal events ($p < 0.0001$) compared with placebo [83]. When combined with CCBs, indapamide plus perindopril was associated with a 28% reduction in the all-cause mortality risk (RR 0.72, 95% CI 0.57–0.90) compared with a 5% reduction in those without CCB (RR 0.95, 95% CI 0.80–1.12; $p = 0.02$ for homogeneity) [84]. In addition, the PERSUADE substudy of diabetic patients from the EUROPA study showed that perindopril was associated with a nonsignificant 19% reduction in the risk of cardiovascular death, nonfatal MI, or resuscitated cardiac arrest compared with placebo over a median follow-up of 4.3 years, similar to that observed in the overall EUROPA study population [85]. Of note, the prevalence of hypertension in these patients was significantly higher than in the overall study population (39% versus 27%) [85].

Among patients with T2D and nephropathy in the RENAAL study, most of whom were receiving antihypertensive therapy at baseline, the ARB losartan significantly reduced the risk of end-stage renal disease ($p = 0.002$) and hospitalization for HF ($p = 0.005$) compared with placebo, but there were no differences in cardiovascular or all-cause mortality rates [86]. Similarly, irbesartan reduced the relative risk of doubling of serum creatinine compared with placebo ($p = 0.009$) in the IDNT study in hypertensive patients with T2D and nephropathy, but showed no difference in the risk of all-cause death or cardiovascular events [87]. In the IRMA-2 study in hypertensive patients with T2D and microalbuminuria, irbesartan significantly reduced the risk of diabetic nephropathy compared with placebo ($p < 0.001$), but there was no significant difference in the incidence of nonfatal cardiovascular events ($p = 0.11$) [88]. The ORIENT study in patients with T2D, most of whom were on baseline antihypertensive therapy, found a significant reduction in the risk of the cardiovascular composite outcome with olmesartan versus placebo after adjusting for age, cardiovascular history, and albumin-to-creatinine ratio ($p = 0.039$), but no difference in the risk of cardiovascular mortality, all-cause mortality, or renal outcomes [89]. The ROADMAP study in T2D patients with at least one other cardiovascular risk factor (who had a range of BP values) even suggested a possible increase in the risk of cardiovascular death with olmesartan versus placebo [90].

A systematic review and meta-analysis of 13 RCTs in patients with hypertension and T2D ($N = 47{,}008$) found that ACEis were associated with significant reductions in all-cause mortality (OR 0.87, 95% CI 0.80–0.94; $p = 0.0008$; $I^2 = 50\%$) and cardiovascular mortality (OR 0.81, 95% CI 0.68–0.98; $p = 0.03$; $I^2 = 61\%$) compared with placebo, whereas ARBs showed no significant reduction in these outcomes [91].

3 Recommended RAASi Therapy: Hypertension Guidelines

A summary of the international guideline recommendations for the pharmacologic treatment of hypertension is presented in Table 2.

All international guidelines for hypertension management include ACEis and ARBs as first-line treatment options for patients with hypertension [11, 21, 55, 92–95]. An SPC comprising an ACEi or ARB (plus a CCB or diuretic) is recommended by the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) [11], Hypertension Canada [93], the International Society of Hypertension (ISH) [94], and the Latin American Society of Hypertension (LASH) guidelines [21]. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines also recommend SPCs to improve treatment adherence [55].

Initial combination therapy with two first-line agents is recommended in patients with stage 2 hypertension by the ACC/AHA [55] and in most hypertensive patients by the ESC/ESH [11]. The LASH recommend combination therapy in patients with grade 2 or 3 hypertension [21].

For patients with uncomplicated hypertension (i.e., no other cardiovascular comorbidities), none of the international guidelines for hypertension management give a preference for first-line treatment between ACEis and ARBs. The ESC/ESH guidelines state that both classes of RAASi agent have similar effectiveness with regard to major cardiovascular events and mortality [11]. The most recent guidelines from the World Health Organization (WHO) consider both ACEis or ARBs among first-line treatment options, despite limited evidence in terms of head-to-head comparisons for cardiovascular endpoints [95]. In comparison, the ISH guidelines state that the benefits of ACEis and ARBs in RCTs vary in different patient populations, and that the choice of agent should depend on patient characteristics, availability, costs, and tolerability [94].

Table 2 Summary of international guideline recommendations for the pharmacological treatment of hypertension

Guidelines	Preferred RAASi	Other antihypertensive drugs
ACC/AHA [55]	First-line agents for initial therapy include ACEis or ARBs (I, A)	Thiazide diuretics, CCBs
ESC/ESH [11]	Antihypertensive therapy should include ACEis or ARBs (I, A) ARBs may be preferred in patients of Black-African descent due to risk of angioedema with ACEis ARBs are associated with lower rates of treatment discontinuation for AEs	β-blockers, CCBs, or diuretics combined with either ACEi or ARB
Hypertension Canada [93]	Diastolic hypertension (± systolic hypertension) Monotherapy with ACEis or ARBs (Grade B) OR an SPC of an ACEi + CCB (Grade A), an ARB + CCB (Grade B), or an ACEi or ARB + diuretic (Grade B)	Diuretics, β-blockers (patients aged <60 years), long-acting CCBs
	Isolated systolic hypertension without other indications ARBs (Grade B)	Thiazide/thiazide-like diuretics, long-acting dihydropyridine CCBs
ISH [94]	ACEi or ARB (in an SPC with dihydropyridine CCB) Benefits of ACEis and ARBs in RCTs varied between different patient populations Choice between RAASi drug will depend on patient characteristics and drug availability, costs, and tolerability	Dihydropyridine CCB (in combination with ACEi or ARB)
LASH [21]	Grade 1 hypertension Monotherapy with ACEis or ARBs (low CV risk) OR an SPC with ACEi or ARB + CCB or diuretic (moderate or high CV risk)	Diuretics, CCBs, or β-blockers
	Grade 2 or 3 hypertension Combination therapy is recommended, regardless of CV risk	
NICE [92]	Step 1 ACEis or ARBs in hypertensive adults who: (a) have diabetes and are of any age or family origin; OR (b) are aged < 55 years but not of Black-African or African-Caribbean descent	CCBs [hypertensive patients aged ≥ 55 years without diabetes or who are of Black-African or African-Caribbean descent without diabetes (any age)]
	Step 2 ACEis or ARBs plus another antihypertensive drug	CCB or thiazide-like diuretic may be added
WHO [95]	ACEis or ARBs Combination therapy, preferable as an SPC, is recommended as initial therapy to improve adherence	Diuretics (thiazide or thiazide-like) or long-acting dihydropyridine CCBs

ACC American College of Cardiology, *ACEi* angiotensin-converting enzyme inhibitor, *AE* adverse event, *AHA* American Heart Association, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *CV* cardiovascular, *ESC* European Society of Cardiology, *ESH* European Society of Hypertension, *ISH* International Society of Hypertension, *LASH* Latin American Society of Hypertension, *NICE* National Institute for Health and Care Excellence, *RAASi* renin–angiotensin–aldosterone system inhibitor, *RCT* randomized clinical trial, *SPC* single-pill combination, *WHO* World Health Organization

With regard to tolerability, the ESC/ESH guidelines mention that ARBs have lower rates of treatment discontinuation for adverse events than ACEis, and may be preferred in patients of Black-African descent due to an increased risk of angioedema with ACEis [11]. Similarly, guidelines from Hypertension Canada [93] and the National Institute for Health and Care Excellence (NICE) [92] state that ARBs are preferred over ACEis in Black patients. The NICE guidelines state that ARBs should be used in patients who do not tolerate ACEis (e.g., due to cough) [92].

According to the guidelines, the combination of ACEis and ARBs is not recommended [11, 55, 92, 93]. This is because the combination of two RAASi agents has been associated with an increased risk of hypotension and hyperkalemia [63, 96].

4 Recommended RAASi Therapy: Cardiovascular Guidelines

A summary of the international cardiovascular guideline recommendations for pharmacologic treatment in patients with hypertension and other comorbidities is provided in Table 3.

Table 3 Summary of international cardiovascular guideline recommendations for pharmacologic treatment in patients with hypertension and other comorbidities

Comorbidity guideline	Preferred RAASi	Other antihypertensive drugs
CVD prevention		
ESC [97]	RAASi (ACEi or ARB) with a CCB or diuretic (I, A)	Other combinations of ACEis, ARBs, β-blockers, CCBs, and thiazide/thiazide-like diuretics can be used
CAD		
AHA/ACC/ASH [20]	ACEis should be prescribed in all CAD patients with stable angina who have hypertension, diabetes, LVEF ≤ 40%, or CKD unless contraindicated (I, A) ARBs are recommended in these patients if ACEis not tolerated (I, A)	β-blockers, CCBs, thiazide or thiazide-like diuretics, and (in selected patients) MRAs
LASH [21]	ACEis are recommended as a first-line option in patients with recent MI	β-blockers (in patients with CAD)
Acute STEMI		
ACC/AHA [19]	ACEis should be started within 24 h to all STEMI patients with anterior infarction, HF, or LVEF ≤ 40%, unless contraindicated (I, A) ARBs should be given in these patients if ACEis not tolerated (I, B) ACEis are reasonable for all STEMI patients if not contraindicated (IIa, A)	β-blockers and MRAs (if not contraindicated)
ESC [16]	ACEis are recommended, starting within first 24 h of STEMI in patients with HF, LV systolic dysfunction, diabetes, or anterior infarct (I, A) ARBs (preferably valsartan) can be used if ACEis are not tolerated (I, B) ACEis should be considered in all patients in the absence of contraindications (IIa, A)	β-blockers, MRAs (except for patients with renal failure or hyperkalemia)
Non-STEMI ACS		
AHA/ACC [13]	Start ACEis and continue indefinitely in all patients with LVEF ≤40% and those with hypertension, diabetes, or stable CKD, unless contraindicated (I, A) ARBs are recommended in patients with HF or MI with LVEF ≤40% if ACEis not tolerated (I, A) ARBs are reasonable in other patients with cardiac or other vascular disease who are ACEi intolerant (IIa, B) ACEis may be reasonable in all other patients with cardiac or other vascular disease (IIb, B)	β-blockers, nondihydropyridine CCBs, MRAs (if not contraindicated)
ESC [14]	ACEis (or ARBs if ACEis not tolerated) are recommended in patients with HFrEF, diabetes, or CKD (unless contraindicated) to reduce all-cause and CV mortality and CV morbidity (I, A)	β-blockers (in patients with systolic LV dysfunction, HFrEF, or prior MI) and MRAs (in patients with HFrEF)
CCS		
ESC [17]	ACEis (or ARBs) are recommended in patients with hypertension, HF, or diabetes (I, A) ACEis should be considered in CCS patients at very high risk of CV events (IIa, A)	β-blockers (in patients with previous STEMI, LV dysfunction, or systolic HF)
Acute or chronic HF		
AHA/ACC/HFSA [15]	HFrEF ACEis are recommended in patients with chronic HFrEF if ARNi not tolerated (I, A) ARBs is recommended if ACEis not tolerated (I, A)	ARNi (in patients with NYHA II–III symptoms), β-blockers, MRAs (in patients with NYHA II–IV symptoms)

Table 3 (continued)

Comorbidity guideline	Preferred RAASi	Other antihypertensive drugs
	HFpEF ARBs may be considered in selected patients to decrease hospitalizations, particularly those with low LVEF (2b, B-R)	Diuretics (as needed), ARNi or MRAs
ESC [18]	HFrEF ACEis are recommended to reduce the risk of HF hospitalization and death (I, A) ARBs are recommended (with β-blocker and MRA) in symptomatic patients intolerant to ACEis or ARNis (I, B)	β-blockers, MRAs, or diuretics
	HFpEF ACEis or ARBs Optimal hypertension treatment strategy is uncertain	β-blockers, CCBs, and diuretics
LASH [21]	ACEis are preferable as first choice antihypertensive treatment	Diuretics, β-blockers, or MRAs
Diabetes		
ADA [98]	ACEis or ARBs recommended as first-line therapy for hypertension in patients with diabetes and CAD	Thiazide-like diuretics, dihydropyridine CCBs, or MRAs (in patients with resistant hypertension)
ESC [99]	ACEis or ARBs are recommended, particularly in patients with hypertension, microalbuminuria, albuminuria, proteinuria, or LVH (I, A) ACEis are recommended to prevent major CV events in all patients with CCS or ACS and systolic LV dysfunction; an ARB should be administered in patients intolerant to ACEis	CCBs, thiazide/thiazide-like diuretics
LASH [21]	ACEis or ARBs in patients with diabetes or metabolic syndrome	
CKD		
ACC/AHA [55]	ACEis should be considered to slow kidney disease progression (IIa, B-R) ARBs may be considered if ACEis not tolerated (IIb, C-EO)	
ESC [11]	ACEis or ARBs are recommended in patients with microalbuminuria or proteinuria (I, A)	Add CCB or diuretic to RAASi
KDIGO [100]	ACEis or ARBs in patients with hypertension and proteinuria	Direct renin inhibitor or MRAs (if ACEis or ARBs not tolerated), non-dihydropyridine CCBs, β-blockers, diuretics, and α1-blockers
LASH [21]	ACEis or ARBs are preferable as first choice of antihypertensive therapy	

ACC American College of Cardiology, *ACEi* angiotensin-converting enzyme inhibitor, *ACS* acute coronary syndrome, *ADA* American Diabetes Association, *AHA* American Heart Association, *ARB* angiotensin receptor blocker, *ARNi* angiotensin receptor–neprilysin inhibitor, *ASH* American Society of Hypertension, *CAD*, coronary artery disease, *CCB* calcium channel blocker, *CCS* chronic coronary syndrome, *C-EO* consensus or expert opinion based on clinical experience, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *ESC* European Society of Cardiology, *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HFSA* Heart Failure Association of America, *KDIGO* Kidney Disease: Improving Global Outcomes, *LASH* Latin American Society of Hypertension, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *MI* myocardial infarction, *MRA* mineralocorticoid receptor antagonist, *NYHA* New York Heart Association, *RAASi* renin–angiotensin–aldosterone system inhibitor, *STEMI* ST-segment elevation myocardial infarction

4.1 Cardiovascular Disease Prevention

The ESC guidelines for CVD prevention recommend treatment with an ACEi or ARB in combination with a CCB or diuretic to manage hypertension [97]. Although the CVD prevention guidelines do not specify a preference for ACEis over ARBs, most other cardiovascular guidelines preferably recommend ACEis as first-line treatment, with ARBs recommended for patients who are unable to tolerate an ACEi [13–21].

4.2 Coronary Syndromes

4.2.1 Coronary Artery Disease

In hypertensive patients with CAD, acute STEMI, or non-STEMI ACS, AHA/ACC/American Society of Hypertension (ASH), ESC, and LASH guidelines recommend ACEis as the first-line treatment option [13, 14, 16, 19–21]. In these guidelines, ARBs are recommended in patients who are unable to tolerate ACEis. These recommendations are based (at least in part) on the results of the HOPE study in patients with high cardiovascular risk (described above) [58].

4.2.2 Acute Coronary Syndrome

In patients with non-STEMI ACS, the ESC guidelines recommend ACEis (or ARBs in patients with intolerance to ACEis) in patients with HFrEF (LVEF < 40%), diabetes, or CKD (unless contraindicated) to reduce cardiovascular morbidity and all-cause and cardiovascular mortality [14]. Similarly, the AHA/ACC guidelines recommend initiating and continuing ACEi therapy indefinitely in all patients with LVEF ≤ 40% and those with hypertension, diabetes, or stable CKD, unless contraindicated [13].

In patients with acute STEMI, both the ESC [16] and the ACC/AHA [19] guidelines recommend starting ACEis within 24 h of STEMI in patients with HF or LVEF ≤ 40%, or ARBs in patients who do not tolerate ACEis.

4.2.3 Chronic Coronary Syndromes

In patients with chronic coronary syndromes (CCS) and concurrent hypertension, the ESC guidelines recommend considering ACEis (or ARBs in patients with intolerance) [17]. These recommendations are based on the results of the SAVE and SOLVD studies (described above) [68, 76]. These guidelines also state that ACEis should also be considered in patients with CCS who are at very high risk of adverse cardiovascular events [17].

4.2.4 Heart Failure

In patients with HFrEF, ACEis are recommended by the AHA/ACC/Heart Failure Society of America (HFSA) [15], ESC [18], and LASH [21] guidelines. The ESC guidelines recommend ARBs to reduce the risk of cardiovascular death and hospitalization for HF in symptomatic patients who are unable to tolerate ACEis or angiotensin receptor-neprilysin inhibitors; these patients should also receive a β-blocker and a mineralocorticoid receptor antagonist and SGLT2 inhibitors [18]. However, the optimal hypertension strategy in patients with HF with preserved ejection fraction is less certain; both ACEis or ARBs are recommended by the American and European guidelines [15, 18].

4.3 Type 2 Diabetes

In contrast to other cardiovascular comorbidities, most guidelines for the management of patients with T2D recommend ACEis or ARBs as first-line treatment for hypertension, with no preference for one RAASi over another, including those from the American Diabetes Association [98] and LASH [21]. However, the ESC guidelines state that ACEis should be used in the management of hypertension (or ARBs in patients who are intolerant to ACEis), and recommend ACEis to prevent major cardiovascular events in all patients with CCS or ACS and systolic LV dysfunction [99].

4.4 Chronic Kidney Disease

In patients with CKD, the ACC/AHA guidelines for management of hypertension recommend ACEis as first-line treatment to slow the progression of kidney disease [55]. However, the ESC, Kidney Disease: Improving Global Outcomes (KDIGO) and LASH guidelines do not differentiate between the use of ACEis and ARBs in patients with microalbuminuria or proteinuria [11, 21, 100].

5 Which Guideline Should be Applied in Daily Clinical Practice?

The international guidelines for hypertension management do not differentiate between ACEis and ARBs in their recommendations for first-line treatment (Table 2). However, the ISH 2020 guidelines acknowledge that the benefits of ACEis and ARBs in RCTs vary in different patient populations [94], and the Hypertension Canada guidelines state a preference for ACEi in certain patients, including those with recent MI, HF, prior stroke or TIA, or CKD [93].

The observed differences in effects with regard to cardiovascular and renal morbidity and mortality outcomes in RCTs may be attributed to differences in the mechanisms of action between ACEis (Fig. 1) and ARBs (Fig. 2). It is thought that the increased bradykinin levels, potentiated bradykinin response, and stimulated nitric oxide production are responsible for the cardiovascular and renal protective effects observed during ACEi treatment [34]. Therefore, it may be more appropriate to consider ACEis and ARBs as different classes of antihypertensive drugs within the same RAASi group.

In daily clinical practice, most patients with hypertension will have other hypertension-related comorbidities, but these comorbidities do not change the need to manage and control their underlying hypertension. In contrast to the hypertension guidelines, most guidelines for CVD (i.e., for CAD, acute STEMI, non-STEMI ACS, CCS, or acute or chronic HF), T2D, and CKD preferably recommend ACEis over ARBs to manage hypertension, with ARBs considered as an alternative when ACEis are not tolerated (Table 3). These recommendations are based on the RCT evidence in patients with these comorbidities (described above). Regardless of the patient's cardiovascular risk level or comorbidities, the first goal of hypertension management should be to decrease BP. If all classes of antihypertensive medications are available, physicians could consider the most appropriate option, while taking the patient's residual cardiovascular risk into account, as some patients will remain at risk even with adequate BP control. Given the evidence from RCTs and meta-analyses for the cardiovascular and renal benefits of ACEis over ARBs across several patient populations, we may conclude that ACEis could be considered as a first-line treatment for hypertension, especially in patients at high cardiovascular risk or with cardiovascular comorbidities.

6 Conclusions

When treating patients with hypertension or other cardiovascular comorbidities, the cardiovascular and renal protective effects of RAASis should be taken into account when choosing the most appropriate first-line antihypertensive treatment. For hypertensive patients without any comorbidities, the international guidelines do not differentiate between ACEis and ARBs as first-line treatment. In contrast, in patients with other cardiovascular or metabolic disorders (with or without hypertension), the international guidelines recommend ACEis as first-line treatment, as the available evidence suggests that ACEis provide additional benefits beyond BP control with regard to reduction in cardiovascular risk and mortality in these patients.

Acknowledgments We would like to thank Sarah Greig, PhD, CMPP, of Springer Healthcare Communications who provided medical writing assistance in the preparation of the outline and subsequent drafts of this manuscript, and post-submission editorial assistance. This medical writing assistance was funded by Servier.

Declarations

Funding Open access publication was funded by Servier. Medical writing assistance in the preparation of this manuscript was funded by Servier.

Conflict of Interest Luis Alcocer: Honoraria as consultant from MSD, Menarini, Novartis, Pfizer, Sanofi-Aventis, Servier, Silanes, Stendhal, Takeda, and Viatris; honoraria for presentations and involvement in educational seminars from Asofarma, AstraZeneca, Bayer, Daichi-Sankyo, MSD, Menarini, Novartis, Pfizer, Sanofi-Aventis, Servier, Silanes, Stendhal, Takeda, and Viatris. Alfonso Bryce: Honoraria for lectures from Abbott, AstraZeneca, Bayer, Biotoscana, Boehringer Ingelheim, Bristol Myers Squibb, Emcure, Farmakonsuma, Farmindustria, GlaxoSmithKline, Grupo Farma, Megalabs, Menarini, Merck Serono, MSD, Novartis, OM Pharma, Pfizer, Roemmers, Sanofi-Aventis, Servier, Schering-Plough, Tecnofarma, and Teva; research grants from Abbott, GlaxoSmithKline, MSD, Novartis, and Takeda; personal fees for advisory board participation from Abbott, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Novartis, and Pfizer; and honoraria as consultant from Servier. David de Padua Brasil: Served as the NLI (Brazil) and reports institutional grants from Bayer during the conduct of the Voyager PAD clinical trial; honoraria as consultant from Servier and Libbs; personal fees to write scientific educational materials, participate in scientific boards, and speak in educational meetings/seminars from Libbs and Servier; travel grants to cover transport, hotel accommodations, and registration fee to attend international educational congresses from Servier; and personal fees to speak at scientific meetings organized/sponsored by Viatris, Biolab, Bayer, and Bristol Myers Squibb. Joffre Lara: Honoraria for presentations and involvement in educational seminars from Servier, Astra Zeneca, Novartis, Boehringer Ingelheim, Novo Nordisk, Merck, Medicamenta, and Megalabs. Javier Moreno Cortes: Honoraria for presentations and involvement in educational seminars from Servier. Daniel Quesada: Honoraria for presentations and involvement in educational seminars from Servier, AstraZeneca, Pfizer, and Novartis; consultation fees from Pfizer, Servier, AstraZeneca, and Merck; and educational and travel grants from Bayer, Ferrer, and Astra Zeneca. Pablo Rodriguez: Honoraria for consultations, presentations, and involvement in educational seminars from Servier, Bagó, Baliarda, Gador, and Raffo; and travel grants from Servier, Bagó, and Baliarda.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Materials Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this manuscript.

Code Availability Not applicable.

Author Contributions PR and LA contributed to the conceptualization of the review article, bibliography search, and review and editing of manuscript. All authors critically revised the outline and subsequent drafts of the manuscript, and approved the final version.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398(10304):957–80.
2. Zhou B, Perel P, Mensah GA, et al. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat Rev Cardiol. 2021;18(11):785–802.
3. Poulter NR, Borghi C, Damasceno A, et al. May Measurement Month 2019: results of blood pressure screening from 47 countries. Eur Heart J Suppl. 2021;23(Suppl B):B1–5.
4. Blood Pressure Lowering Treatment Trialists Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. Lancet. 2021;397(10285):1625–36.
5. Zhang W, Zhang S, Deng Y, et al. Trial of intensive blood-pressure control in older patients with hypertension. N Engl J Med. 2021;385(14):1268–79.
6. Wright JT Jr, Williamson JD, The SPRINT Research Group, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.
7. Jaeger BC, Bress AP, Bundy JD, et al. Longer-term all-cause and cardiovascular mortality with intensive blood pressure control: a secondary analysis of a randomized clinical trial. JAMA Cardiol. 2022;7(11):1138–46.
8. Kontis V, Cobb LK, Mathers CD, et al. Three public health interventions could save 94 million lives in 25 years. Circulation. 2019;140(9):715–25.
9. Whelton PK, Carey RM, Mancia G, et al. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension guidelines: comparisons, reflections, and recommendations. Circulation. 2022;146(11):868–77.
10. Parati G, Kjeldsen S, Coca A, et al. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021;77(2):692–705.
11. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104.
12. Maddox TM, Januzzi JL Jr, Writing Committee, et al. 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2017;77(6):772–810.
13. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(25):e344-426.
14. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289–367.
15. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895–1032.
16. Ibánez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119–77.
17. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–77.
18. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726.
19. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362-425.
20. Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Hypertension. 2015;65(6):1372–407.
21. Task Force of the Latin American Society of Hypertension. Guidelines on the management of arterial hypertension and related comorbidities in Latin America. J Hypertens. 2017;35(8):1529–45.
22. Heran BS, Wong MM, Heran IK, et al. Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. Cochrane Database Syst Rev. 2008;4:CD003823.
23. Heran BS, Wong MM, Heran IK, et al. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev. 2008;4:CD003822.
24. Baker WL, Coleman CI, Kluger J, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. Ann Intern Med. 2009;151(12):861–71.
25. Savarese G, Costanzo P, Cleland JG, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. J Am Coll Cardiol. 2013;61(2):131–42.
26. van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J. 2012;33(16):2088–97.
27. Wei J, Galaviz KI, Kowalski AJ, et al. Comparison of cardiovascular events among users of different classes of antihypertension medications: a systematic review and network meta-analysis. JAMA Netw Open. 2020;3(2): e1921618.

28. Brugts JJ, van Vark L, Akkerhuis M, et al. Impact of renin-angiotensin system inhibitors on mortality and major cardiovascular endpoints in hypertension: a number-needed-to-treat analysis. Int J Cardiol. 2015;181:425–9.
29. Wong ND, Lopez VA, L'Italien G, et al. Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003–2004. Arch Intern Med. 2007;167(22):2431–6.
30. Lévy BI, Mourad JJ. Renin angiotensin blockers and cardiac protection: from basis to clinical trials. Am J Hypertens. 2022;35(4):293–302.
31. Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. Am J Hypertens. 1999;12(S9):205S–13S.
32. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation. 1998;97(14):1411–20.
33. Dezsi CA, Szentes V. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on prothrombotic processes and myocardial infarction risk. Am J Cardiovasc Drugs. 2016;16(6):399–406.
34. Ancion A, Tridetti J, Nguyen Trung ML, et al. A review of the role of bradykinin and nitric oxide in the cardioprotective action of angiotensin-converting enzyme inhibitors: focus on perindopril. Cardiol Ther. 2019;8(2):179–91.
35. Sanders GD, Coeytaux R, Dolor RJ, et al. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), and direct renin inhibitors for treating essential hypertension: an update. Rockville: Agency for Healthcare Research and Quality (US); 2011.
36. Barreras A, Gurk-Turner C. Angiotensin II receptor blockers. Proc (Bayl Univ Med Cent). 2003;16(1):123–6.
37. Schmieder RE. Mechanisms for the clinical benefits of angiotensin II receptor blockers. Am J Hypertens. 2005;18(5):720–30.
38. Allen AM, Zhuo J, Mendelsohn FA. Localization and function of angiotensin AT1 receptors. Am J Hypertens. 2000;13(1 Pt 2):31S–8S.
39. Wu L, Iwai M, Nakagami H, et al. Roles of angiotensin II type 2 receptor stimulation associated with selective angiotensin II type 1 receptor blockade with valsartan in the improvement of inflammation-induced vascular injury. Circulation. 2001;104(22):2716–21.
40. Allen TJ, Cao Z, Youssef S, et al. Role of angiotensin II and bradykinin in experimental diabetic nephropathy. Functional and structural studies. Diabetes. 1997;46(10):1612–8.
41. Ito T, Yamakawa H, Bregonzio C, et al. Protection against ischemia and improvement of cerebral blood flow in genetically hypertensive rats by chronic pretreatment with an angiotensin II AT1 antagonist. Stroke. 2002;33(9):2297–303.
42. Dandona P, Dhindsa S, Ghanim H, et al. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. J Hum Hypertens. 2007;21(1):20–7.
43. Müller P, Kazakov A, Jagoda P, et al. ACE inhibition promotes upregulation of endothelial progenitor cells and neoangiogenesis in cardiac pressure overload. Cardiovasc Res. 2009;83(1):106–14.
44. Ceconi C, Fox KM, Remme WJ, et al. ACE inhibition with perindopril and endothelial function. Results of a substudy of the EUROPA study: PERTINENT. Cardiovasc Res. 2007;73(1):237–46.
45. Benicky J, Sanchez-Lemus E, Pavel J, et al. Anti-inflammatory effects of angiotensin receptor blockers in the brain and the periphery. Cell Mol Neurobiol. 2009;29(6–7):781–92.
46. Sanchez-Lemus E, Murakami Y, Larrayoz-Roldan IM, et al. Angiotensin II AT1 receptor blockade decreases lipopolysaccharide-induced inflammation in the rat adrenal gland. Endocrinology. 2008;149(10):5177–88.
47. Awad K, Zaki MM, Mohammed M, et al. Effect of the renin-angiotensin system inhibitors on inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc. 2022;97(10):1808–23.
48. Nakamura T, Kawachi K, Saito Y, et al. Effects of ARB or ACE-inhibitor administration on plasma levels of aldosterone and adiponectin in hypertension. Int Heart J. 2009;50(4):501–12.
49. Sriramula S, Francis J. Tumor necrosis factor - alpha is essential for angiotensin II-induced ventricular remodeling: role for oxidative stress. PLoS ONE. 2015;10(9): e0138372.
50. Mehta JL, Li DY, Yang H, et al. Angiotensin II and IV stimulate expression and release of plasminogen activator inhibitor-1 in cultured human coronary artery endothelial cells. J Cardiovasc Pharmacol. 2002;39(6):789–94.
51. Collet JP, Montalescot G, Vicaut E, et al. Acute release of plasminogen activator inhibitor-1 in ST-segment elevation myocardial infarction predicts mortality. Circulation. 2003;108(4):391–4.
52. Kim MP, Zhou M, Wahl LM. Angiotensin II increases human monocyte matrix metalloproteinase-1 through the AT2 receptor and prostaglandin E2: implications for atherosclerotic plaque rupture. J Leukoc Biol. 2005;78(1):195–201.
53. Esteban V, Ruperez M, Sanchez-Lopez E, et al. Angiotensin IV activates the nuclear transcription factor-kappaB and related proinflammatory genes in vascular smooth muscle cells. Circ Res. 2005;96(9):965–73.
54. Yang H, Zeng XJ, Wang HX, et al. Angiotensin IV protects against angiotensin II-induced cardiac injury via AT4 receptor. Peptides. 2011;32(10):2108–15.
55. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension. 2018;71(6):1269–324.
56. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887–98.
57. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens. 2003;21(5):875–86.
58. Yusuf S, Sleight P, Heart Outcomes Prevention Evaluation Study Investigators, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342(3):145–53.
59. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895–906.
60. Yusuf S, Teo K, Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008;372(9644):1174–83.
61. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363(9426):2022–31.
62. McMurray JJ, Holman RR, NAVIGATOR Study Group, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010;362(16):1477–90.

63. Yusuf S, Teo KK, ONTARGET Investigators, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547–59.
64. US Food and Drug Administration. Micardis (telmisartan) tablets, for oral use: US prescribing information. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020850s045lbl.pdf. Accessed 23 Feb 2023.
65. EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362(9386):782–8.
66. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004;351(20):2058–68.
67. Pitt B, O'Neill B, Feldman R, et al. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. Am J Cardiol. 2001;87(9):1058–63.
68. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327(10):669–77.
69. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993;342(8875):821–8.
70. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995;333(25):1670–6.
71. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med. 1995;332(2):80–5.
72. Swedberg K, Held P, Kjekshus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med. 1992;327(10):678–84.
73. Dickstein K, Kjekshus J, OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet. 2002;360(9335):752–60.
74. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349(20):1893–906.
75. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429–35.
76. Yusuf S, Pitt B, SOLVD Investigators, et al. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293–302.
77. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362(9386):772–6.
78. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345(23):1667–75.
79. Jong P, Demers C, McKelvie RS, et al. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2002;39(3):463–70.
80. Tai C, Gan T, Zou L, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2017;17(1):257.
81. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358(9287):1033–41.
82. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med. 2008;359(12):1225–37.
83. Patel A, MacMahon S, ADVANCE Collaborative Group, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370(9590):829–40.
84. Chalmers J, Arima H, Woodward M, et al. Effects of combination of perindopril, indapamide, and calcium channel blockers in patients with type 2 diabetes mellitus: results from the Action In Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) trial. Hypertension. 2014;63(2):259–64.
85. Daly CA, Fox KM, Remme WJ, et al. The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy. Eur Heart J. 2005;26(14):1369–78.
86. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–9.
87. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851–60.
88. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345(12):870–8.
89. Imai E, Chan JC, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. Diabetologia. 2011;54(12):2978–86.
90. Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011;364(10):907–17.
91. Iv X, Zhang Y, Niu Y, et al. Comparison of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular outcomes in hypertensive patients with type 2 diabetes mellitus: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2018;97(15): e0256.
92. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. 2019. https://www.nice.org.uk/guidance/ng136/resources/hypertension-in-adults-diagnosis-and-management-pdf-66141722710213. Accessed 23 Feb 2023.
93. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. Can J Cardiol. 2020;36(5):596–624.

94. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension. 2020;75(6):1334–57.
95. World Health Organization. Guidelines for the pharmacological treatment of hypertension in adults. 2021. https://apps.who.int/iris/bitstream/handle/10665/344424/9789240033986-eng.pdf. Accessed 23 Feb 2023.
96. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369(20):1892–903.
97. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.
98. American Diabetes Association Professional Practice Committee. 11 Chronic kidney disease and risk management: Standards of Medical Care in Diabetes—2023. Diabetes Care. 2022;46(Suppl_1):S191–202.
99. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323.
100. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1–276.