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REVIEW

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Pharmacotherapies for essential hypertension: an in-depth review

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ABSTRACT

Hypertension, a widespread global health concern affecting a staggering 1.28 billion adults, poses a significant challenge due to its silent nature and inadequate management rates. This article provides an evidence-based approach to common pharmacotherapies for essential hypertension, analyzing their efficacy and safety. We will explore guidelines on target blood pressure goals and discuss first-line agents such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin 2 receptor blockers (ARBs), calcium channel blockers (CCBs), thiazide diuretics, and beta-blockers. The review highlights emerging evidence on combination therapies and addresses adverse effects. The objective of this comprehensive overview is to provide guidance for clinical decision-making and enhance patient outcomes.

KEYWORDS

Hypertension; Angiotensin-converting enzyme inhibitors; Calcium channel blockers; Thiazide diuretics; Beta-blockers; Spironolactone

ARTICLE HISTORY

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Introduction

Hypertension is a pervasive global issue, affecting 1.28 billion adults aged 30-79 [1]. There are 46% of adults who remain undiagnosed, and only 21% who are effective in managing their health problems [1]. This silent epidemic extracts a formidable financial toll on the United States, ranging from $131 to $198 billion annually, covering healthcare services, medications, and the economic impact of premature mortality [1]. In the realm of global health objectives, a vital target is reducing hypertension prevalence by 33% between 2010 and 2030 [2]. This underscores the need for a comprehensive review of frontline pharmacotherapies for essential hypertension.

The 2021 WHO guidelines establish distinct blood pressure targets for various hypertensive patient groups. For hypertensive patients without comorbidities, the recommended target is to maintain blood pressure below <140/90 mmHg. However, patients with hypertension and known cardiovascular disease (CVD) are advised to aim for an even lower systolic blood pressure of <130 mmHg. Additionally, high-risk hypertensive individuals, which include those with elevated CVD risk, diabetes mellitus, or chronic kidney disease, are encouraged to achieve a systolic blood pressure goal of <130 mmHg. These tailored blood pressure targets reflect the evolving understanding of hypertension management, emphasizing the importance of individualized care to mitigate cardiovascular risks and complications.

Notably, the ACC defines >130 mmHg as stage I hypertension. A pivotal 2023 NEJM study revealed that among high cardiovascular-risk patients, aiming for a systolic blood pressure <120 mm Hg led to lower rates of major adverse cardiovascular events and reduced all-cause mortality compared to the <140 mm Hg target. However, intensive treatment was associated with higher adverse event rates, including hypotension, syncope, acute kidney injury, and electrolyte imbalances [3].

Approaches in the Presence of Compelling Comorbidities

Expert panels, such as the ACC/AHA and the European Society of Cardiology (ESC), recommend a three-year course of beta-blocker treatment (which includes medications like bisoprolol, carvedilol, metoprolol succinate, metoprolol tartrate, nadolol, propranolol, or timolol) following a heart attack. However, since there haven't been clinical trials specifically evaluating the usefulness of maintaining β-blockers in post-MI patients with normal LVEF, several observational studies have attempted to investigate this matter. Nevertheless, the outcomes have been inconsistent, with some suggesting potential clinical advantages while others have not found any [4].

Lisinopril treatment is associated with decreased proteinuria and improved creatinine clearance [5]. Despite the higher likelihood of experiencing side effects such as hyperkalemia, cough, and hypotension, ACE inhibitors (ACEIs) continue to outperform ARBs and other blood pressure-lowering medications. They offer the greatest advantages in terms of preventing kidney issues, cardiovascular complications, cardiovascular-related deaths, and overall mortality in individuals with non-dialysis chronic kidney disease stages 3 to 5 (CKD3–5). In cases of advanced diabetic kidney disease, ACEIs were found to be more effective than ARBs in reducing the risk of all-cause mortality, although they didn't show the same superiority when it came to kidney and cardiovascular events [6]. The approach to diabetic patients without albuminuria is the same as those without diabetes. Patients with atrial fibrillation (AFib) can derive dual benefits from calcium channel blockers or beta-blocking agents, as these medications not only aid in rate control but also exhibit antihypertensive effects.

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ESC guidelines recommend the following options for the management of stable coronary heart disease (SCHD), increasing beta-blocker doses, adding dihydropyridine calcium channel blockers, incorporating ivabradine, ranolazine, nicorandil, or trimetazidine. In the management of heart failure with reduced EF, beta-blockers, sacubitril-valsartan (Entresto), mineralocorticoid receptor antagonists (MRA), ACE inhibitors, and ARBs all offer potential benefits [6].

Doxazosin has shown notable enhancements in BPH symptoms, irrespective of the initial symptom severity ($P<0.001$). Notably, significant reductions in blood pressure were observed primarily in patient groups with elevated baseline blood pressure. Individuals who initially had poorly managed baseline blood pressure, whether they were not receiving treatment or were mainly using angiotensin-converting enzyme inhibitors or calcium channel blockers, successfully achieved control of their blood pressure (lowering it to less than 140/90 mm Hg) by incorporating doxazosin into their treatment regimen [7].

Table 1 outlines the compelling indications for the use of specific medications in the management of various cardiovascular conditions.

Table 1. Current commercially available ultrasound contrast agents.

Post MI	Beta-blocker, ACE inhibitor or ARB, aldosterone antagonist
Chronic kidney disease with proteinuria	ACE inhibitor or ARB
Atrial fibrillation	Beta-blocker, non-dihydropyridine calcium channel blocker
Heart failure with reduced EF	ARNI, ACE inhibitor or ARB, beta blocker, diuretic, aldosterone Antagonist
BPH	Alpha blocker

MI: myocardial infarction; BPH: benign prostatic hypertrophy; EF: ejection fraction; ACE: Angiotensin-converting enzyme; ARB: angiotensin receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitor

ACE/ARB inhibitor

ACE inhibitors primarily function by impeding the conversion of angiotensin I to angiotensin II. This mechanism leads to a reduction in blood pressure by preventing vasoconstriction and the retention of salt and water induced by aldosterone. The CONSENSUS trial showcased the first ACE inhibitors' efficacy in improving outcomes for patients with NYHA class IV heart failure, significantly reducing mortality rates and extending overall survival by 50% (from 521 to 781 days) [8]. Although blood pressure control wasn't the primary goal, the study underscored ACE inhibitors' potential cardiovascular benefits.

The HOPE trial investigated ramipril, in high-risk patients (age >55, cardiovascular disease, diabetes, hypertension, or high cholesterol) and revealed a significant reduction in cardiovascular events and blood pressure. Among diabetic subjects, the reduction in the combined primary endpoint was even more pronounced, at 25% [9].

In the LIFE trial, it was observed that losartan (an ARB) surpassed atenolol (a beta-blocker) in decreasing the likelihood of stroke and cardiovascular events in hypertensive patients having left ventricular hypertrophy. This underscores the importance of targeting the angiotensin system for controlling blood pressure and reducing cardiovascular risks [10].

Side effects

In the ONTARGET trial, involving 8,576 patients who received ramipril, hypotensive symptoms necessitating drug discontinuation were observed in only 1.7% of cases [11]. Patients who are treated with ACE inhibitors, including medications like ramipril, may experience a reduction in their glomerular filtration rate (GFR). This reduction is typically modest, ranging from around 5 to 25 %, although in some cases, it can be severe, exceeding 30 percent. This effect is more pronounced in individuals with conditions such as bilateral renal artery stenosis, hypertensive nephrosclerosis, heart failure, polycystic kidney disease, or chronic kidney disease [12,13]. For instance, in the ONTARGET trial, which included patients with vascular disease or high-risk diabetes, a severe increase in serum creatinine levels leading to discontinuation of treatment occurred in 0.7% of those taking ramipril and 0.8% taking telmisartan. Additionally, a doubling of serum creatinine was observed in 1.8% of patients taking ramipril and 1.7% of those taking telmisartan [11].

Hyperkalemia, which is characterized by a serum potassium concentration exceeding 5.5 mEq/L, is observed in about 3.3% of patients who are prescribed ACE inhibitors or ARBs. The risk of developing hyperkalemia is higher in individuals with chronic kidney disease, diabetes, those using potassium-retaining medications concurrently, or among older adults [14]. Typically, in patients with relatively normal kidney function, the increase in serum potassium concentration is less than 0.5 mEq/L.

Cough, a frequent side effect associated with ACE inhibitors, was observed in approximately 11% of patients in a meta-analysis that included 125 clinical trials [15]. Angioedema, a rare but potentially life-threatening complication, occurred in 0.3% of patients treated with ramipril in the ONTARGET trial [10]. In the OCTAVE trial involving enalapril, 0.7% of subjects experienced angioedema [16].

Thiazide diuretic

Thiazide diuretics, used to treat hypertension, initially reduce blood pressure through volume loss. They lower plasma volume and cardiac output, leading to a modest blood pressure drop. However, some patients may not respond well due to the activation of the renin-angiotensin system. Long-term, blood pressure decreases as vascular resistance falls despite near-normal plasma volume. The exact mechanism of vasodilation remains uncertain, but it may involve factors like a natriuretic hormone or potassium channel effects. Longer-acting thiazide diuretics, such as chlorthalidone, have a more pronounced vasodilatory effect.

The SHEP study, conducted in 1991, concentrated on adults aged 60 and above who had isolated systolic hypertension. This study demonstrated that treatment with chlorthalidone significantly reduced the risk of stroke, leading to a remarkable 36% reduction, and also lowered the occurrence of cardiovascular events. This highlighted the importance of

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effectively managing high blood pressure in older individuals and had a significant impact on medical guidelines for hypertension management in the elderly [17].

The ALLHAT study, published in December 2002, compared thiazide-type diuretics (chlorthalidone), calcium channel blockers (amlodipine), ACE inhibitors (lisinopril), and alpha-blockers (doxazosin). It found that chlorthalidone was as effective as the other classes in reducing coronary heart disease and heart attack risk. Additionally, chlorthalidone was superior in preventing heart failure [18]. The study influenced the choice of first-line hypertension treatment, highlighting chlorthalidone's effectiveness and leading to its recommendation in guidelines.

Thiazide diuretics can cause hypokalemia, hyponatremia [19], hyperuricemia [20], elevated plasma glucose and cholesterol levels, and magnesium depletion. Low-dose therapy (e.g., 12.5 to 25 mg/day of hydrochlorothiazide or chlorthalidone or 1.25 mg/day of indapamide), commonly used for primary hypertension, has a lower incidence and severity of these side effects [21,22]. High-dose diuretic treatment without a potassium-sparing agent is associated with an increased risk of sudden cardiac death due to these metabolic disturbances [23]. Compared to low doses of hydrochlorothiazide and indapamide, low-dose chlorthalidone carries a greater risk of causing metabolic imbalances [22]. Hyperuricemia, which is induced by loop or thiazide diuretics, can contribute to the development of gout and an increased frequency of gout attacks. The extent of urate retention depends on the dosage of the diuretic used [20].

Calcium channel blockers

Calcium channel blockers (CCBs) function by blocking the movement of extracellular calcium through specialized ion channels within the cell membrane. When this inward flow of calcium is inhibited, it can lead to the relaxation of vascular smooth muscle cells, vasodilation, and a decrease in blood pressure (BP). In cardiac muscle, CCBs cause the reduction of contractility and impede the activity of the sinus pacemaker and atrioventricular conduction velocities. Some examples of dihydropyridine CCBs are nifedipine, amlodipine, and felodipine, while non-dihydropyridine CCBs include verapamil and diltiazem. The Nordic Diltiazem (NORDIL) study published in 2000 was an important clinical trial conducted to investigate the efficacy of diltiazem, in managing hypertension. It compared diltiazem, diuretics, and beta-blockers. The study found that diltiazem demonstrated equal effectiveness in preventing major cardiovascular events such as heart attacks and strokes compared to the traditional treatments of diuretics and beta-blockers. Notably, sub-findings hinted at a potential advantage of diltiazem in reducing stroke risk compared to the other treatments [24]. The ACCOMPLISH (Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients) trial, published in 2008, compared two hypertension treatment approaches. One combined an ACE inhibitor (benazepril) with a calcium channel blocker (amlodipine), while the other combined benazepril with a diuretic (hydrochlorothiazide). Surprisingly, amlodipine proved superior to hydrochlorothiazide in preventing cardiovascular events when used alongside an ACE inhibitor, contrary to the findings of ALLHAT. The ACCOMPLISH study demonstrated that the ACE inhibitor and calcium channel blocker combination reduced cardiovascular events in an older patient population more effectively. The difference in ALLHAT's outcomes may be due to variations between chlorthalidone (used in ALLHAT) and hydrochlorothiazide (used in ACCOMPLISH) in their impact on outcomes beyond blood pressure effects. Alternatively, combining amlodipine with a renin-angiotensin system inhibitor may offer unique benefits compared to amlodipine alone [25].

Dihydropyridines such as amlodipine, felodipine, and nifedipine can induce symptoms like headaches, lightheadedness, flushing, and peripheral edema in as many as 30% of patients [26,27]. On the other hand, non-dihydropyridines like verapamil and diltiazem may cause constipation in about 25% of patients [28]. Additionally, they can lead to bradycardia and a decrease in cardiac output. Due to these potential side effects, such drugs are relatively contraindicated in patients taking beta blockers or those who have heart failure with reduced ejection fraction (HFrEF), sick sinus syndrome, or second or third-degree atrioventricular block.

Peripheral edema risk is higher with dihydropyridines, and it's dose-dependent [29]. Combining these drugs with renin-angiotensin system inhibitors (ACE inhibitors, ARBs, or direct renin inhibitors) can reduce edema occurrence and severity by promoting venodilation and lowering transcapillary pressure [30].

Beta blockers

In elderly patients, especially those without clinical signs of coronary heart disease, beta-blockers, particularly atenolol, are generally deemed ineffective for reducing blood pressure and should not be recommended as a primary preventive measure for cardiovascular disease [31].

In a prospective trial, individuals aged 40-85 who had chronic obstructive pulmonary disease (COPD) were randomly assigned to receive extended-release metoprolol (a beta-blocker) or a placebo. All of these patients had a history of COPD, moderate airflow limitation, and an elevated risk of exacerbations, as demonstrated by a history of exacerbations in the previous year or the prescribed use of supplemental oxygen. The results showed that the time to the first COPD exacerbation was similar between the metoprolol and placebo groups. However, hospitalizations due to exacerbations were more frequent in the metoprolol group [32].

The adverse effects associated with beta-blockers include pharmacological consequences of blocking beta-adrenergic receptors, leading to outcomes such as bronchospasm, hypoglycemia, bradycardia, heart block, intermittent claudication, and Raynaud's phenomenon. Neurological reactions such as depression, fatigue, and nightmares can also occur. Compared to other antihypertensive medications, beta blockers provide less protection against stroke and overall mortality [33]. Additionally, they are linked to impaired glucose tolerance and an increased risk of developing new-onset diabetes, although this risk is lower with vasodilating beta blockers like carvedilol and nebivolol [34,35].

Spironolactone

Spironolactone is a mineralocorticoid receptor antagonist that blocks the actions of aldosterone. It's not the first choice for treating hypertension but is commonly used in patients with treatment-resistant hypertension. International guidelines

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recommend it as a fourth-line therapy for patients whose blood pressure isn't controlled by three other drugs: "A" (ACE inhibitor or ARB), "C" (calcium channel blocker), and "D" (thiazide or thiazide-like diuretic) [36].

The PATHWAY 2 trial established that spironolactone is the most effective fourth-line add-on therapy for drug-resistant hypertension. Bisoprolol or doxazosin is a less effective option for those intolerants to spironolactone. Spironolactone significantly increases the likelihood of achieving blood pressure control, with nearly 60% achieving it within 3 months. However, the study's limitation is its short duration of only 3 months [37].

A meta-analysis by Guo H et al. also supports spironolactone as the best add-on drug for resistant hypertension, indicating sodium retention's primary role. According to the short-term and intermediate-term data from the study, it is suggested that spironolactone is safe and well-tolerated, with some adverse effects like gynecomastia, elevation of serum creatinine, and increase of serum potassium [38].

Comparison between Different Drug Classes

All-cause mortality rates are comparable between first-line RAS (renin-angiotensin system) inhibitors and first-line CCBs (calcium channel blockers), thiazides, and beta-blockers. However, there are variations in some morbidity outcomes. When used as first-line treatment, thiazides led to lower rates of heart failure (HF) and stroke compared to first-line RAS inhibitors. On the other hand, first-line CCBs heightened the risk of heart failure but lowered the risk of stroke as compared to first-line RAS inhibitors, with the increase in heart failure risk being greater than the decrease in stroke risk. There is limited-quality evidence to suggest that when used as first-line treatment, RAS inhibitors reduce the risk of stroke and total cardiovascular (CV) events in comparison to first-line beta-blockers [39].

In older individuals, particularly men, starting antihypertensive treatment with ACE inhibitors appears to yield better outcomes than using diuretic agents, even with similar blood pressure reductions [40].

Table 2 summarizes the adverse effects associated with different classes of antihypertensive medications. Understanding these potential side effects is crucial for healthcare providers when making informed decisions about the choice of medication for hypertension management. Each medication class is linked to specific adverse effects that may impact patient care and treatment outcomes.

Table 2. Adverse effects of antihypertensive medication classes.

ACE inhibitors	Cough Angioedema Hyperkalemia Fetal injury Worsening kidney function in renal artery stenosis or hypovolemia
Thiazide diuretics	Hypokalemia Hyponatremia Hypomagnesemia Hyperuricemia and gout
Dihydropyridine calcium channel	Lower extremity edema Headache Lightheadedness Flushing
Beta-blockers	Bradycardia Bronchospasm Raynaud phenomenon
ARB	Hyperkalemia Fetal injury Worsening kidney function in renal artery stenosis or hypotension
Non-dihydropyridine calcium channel blockers	Bradycardia Constipation
Aldosterone antagonist	Gynecomastia Hyperkalemia Increased serum creatinine

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Combination Therapy *vs.* Sequential Monotherapy

The strongest and most reliable data come from a clinical trial published in JAMA in 2017. In this trial, 605 individuals with hypertension were enrolled and randomly divided into two groups. The first group received initial combination therapy with losartan and hydrochlorothiazide, while the second group received sequential monotherapy. If necessary, individuals in the sequential monotherapy group had the option to transition to combination therapy as well [41]. The study revealed that combination therapy provided a more predictable systolic blood pressure response compared to monotherapy, with no significant difference in adverse events. Consequently, based on these findings, the study recommended initial combination therapy for patients with blood pressure readings exceeding 150/95 mm Hg.

Evidence for combination therapy

The benazepril-amlodipine combo proved superior to benazepril-hydrochlorothiazide in reducing cardiovascular events in high-risk hypertension patients [42]. Calcium channel blockers, besides diuretics, can effectively complement ACE inhibitors, as seen in the accomplish trial.

Telmisartan matched ramipril in vascular disease or high-risk diabetes patients with less angioedema, but combining the two led to more adverse events without added benefits. In sub-Saharan Africa, among black patients, the combination of amlodipine plus hydrochlorothiazide or perindopril was found to be more effective than the combination of perindopril plus hydrochlorothiazide in reducing blood pressure after 6 months of treatment [43].

Conclusions

In the ever-evolving field of hypertension management, selecting an appropriate first-line agent remains a vital decision for healthcare providers. Our comprehensive review has explored the crucial role of various drug classes, including ACE inhibitors, ARBs, CCBs, thiazide diuretics, beta-blockers, and mineralocorticoid receptor antagonists in the treatment of essential hypertension. These agents offer distinct mechanisms of action, addressing the complex pathways that contribute to hypertension. Furthermore, our exploration of combination therapies explains the evidence for strategic synergies for optimizing blood pressure control while minimizing adverse effects. Ultimately, the choice of first-line therapy should be a patient-centered decision, taking into account individual risk factors, comorbidities, and preferences.

Disclosure statement

No potential conflict of interest was reported by the authors.

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