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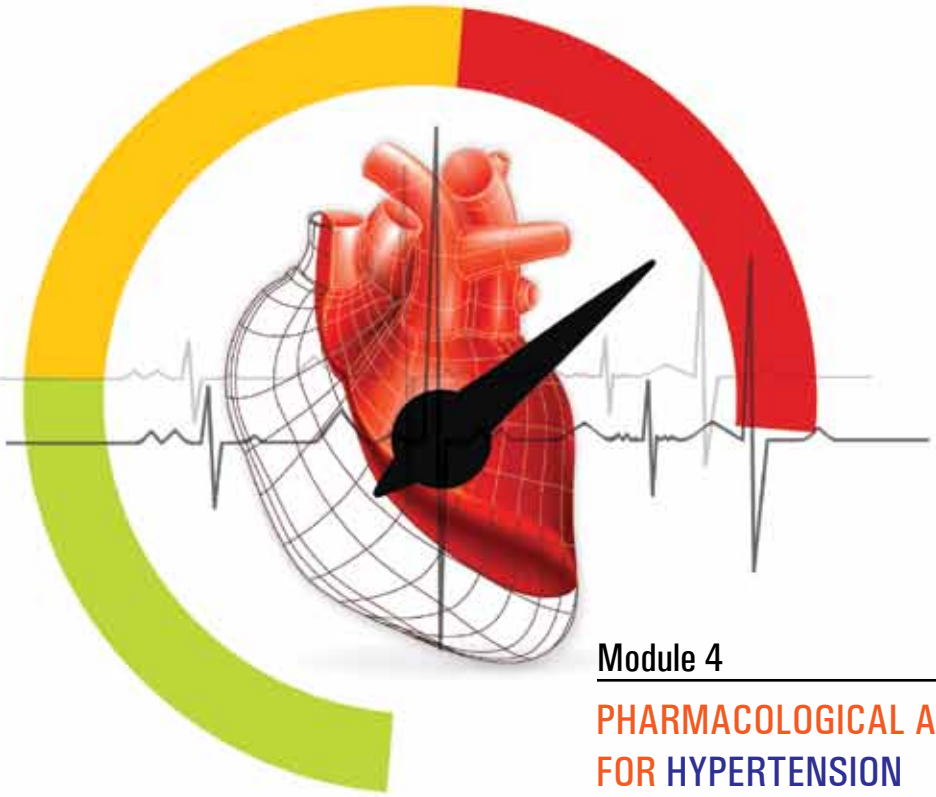
HYPERTENSION



Module 4

PHARMACOLOGICAL APPROACH FOR HYPERTENSION

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Program Information

Need for this program

Hypertension is a widely prevalent disorder, deemed as one of the most prevalent cardiovascular risk factors in both the developed and developing countries. Left untreated, it can predispose to several adverse health consequences, affecting different end organs of the body including the heart, brain, kidneys, and the eyes. Early diagnosis and optimization of blood pressure control is therefore essential. The significance of screening hypertensive patients for end organ damage and comorbid cardiovascular risk factors such as diabetes, and their guidelines-based management cannot be overemphasized. Addressing the relentless rise in burden of hypertension and its associated complications can have a favorable effect in reducing the burden of heart diseases and their associated morbidity and mortality.

Learning objectives

- To update on the current blood pressure cut-off of different stages of hypertension, its diagnosis and management approach
- To familiarize with screening and management approach of end organ complications of hypertension and strategies for their management

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None declared

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Self-assessment criteria and self-assessment threshold

Participants are requested to attempt the self-assessment questionnaire after completing their modules and mail the questionnaire along with the feedback form to: info@cmecom.in. Those participants who successfully attempt the questionnaire with a score of 60% or better will be eligible to receive a CME certificate.

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CONTENTS

PHARMACOLOGICAL APPROACH FOR HYPERTENSION

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OVERVIEW

Hypertension is a major public health challenge worldwide, contributing significantly to cardiovascular (CV) mortality.[1] Blood pressure optimization in hypertensive patients represents a key strategy to reduce risk of CV events, target organ damage (TOD), CV and overall mortality.[1,2] While initial approach to management of hypertension should involve lifestyle changes, particularly stress control, physical exercises and weight management, eventually pharmacological management is required if lifestyle changes alone remain inadequate in reducing blood pressure to goal. Several antihypertensive therapies are currently available. Front-line antihypertensive drug classes include diuretics, renin-angiotensin system (RAS) inhibitors including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs); for list of prominent drugs in each class see back inside page of this module. Beta-blockers are also front-line agents but used specially for managing hypertension associated with acute myocardial infarction (MI), heart failure, and asymptomatic left ventricular hypertrophy (LVH).[1,3] While each of these drugs have well-documented antihypertensive efficacy, a sizable percentage of patients require drugs with different antihypertensive mechanisms in combination to achieve their desired pre-treatment blood pressure goals; in fact, in about 25% of hypertensive patients, three antihypertensive drugs are required in combination to achieve therapeutic targets.[4] Combining two drugs from different classes can afford up to five-times greater reduction in blood pressure compared to doubling the dose of a single drug.[5] In treatment-naïve patients, two antihypertensive drugs in combination should be initiated in those with systolic blood pressure (SBP) >20 mmHg and/or a diastolic blood pressure (DBP) >10 mmHg above the goals, or in those with high CV risk.[4]

AMERICAN AND EUROPEAN HYPERTENSION GUIDELINES: WHEN IS PHARMACOLOGICAL THERAPY RECOMMENDED?

The American College of Cardiology/American Heart Association (ACC/AHA) 2017 guidelines[6] on high blood pressure recommend pharmacological therapy at SBP ≥140 mmHg or DBP ≥90 mmHg in adults with no previous history of CV disease and an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of < 10% for primary CV prevention. On the other hand, they recommend antihypertensive drug therapy in those with CV disease and an average SBP ≥130 mmHg or average

Table 1: Risk categorization (10-year CV risk) - ESC/ESH Guidelines for the management of arterial hypertension

Risk category	Includes
Very high risk	Any of these Documented CV risk either clinical or unequivocal on imaging • Clinical evidence of CV disease • Unequivocal documentation of CV disease on imaging • Diabetes mellitus with evidence of TOD • Severe CKD (eGFR<30ml/min/1.73m^2) • Calculated 10-year SCORE ≥ 10%
High risk	Any of these • Marked elevation of a single risk factor, particularly serum cholesterol > 310 mg/dl, e.g. familial hypercholesterolemia or blood pressure ≥ 180/110 mmHg (grade 3 hypertension) • Any other case of diabetes mellitus (except young individuals with type 1 diabetes without major risk factors) Other categories include: • Moderate CKD (eGFR 30-59 ml/min/1.73m^2) • Hypertensive LVH • Calculated 10-year SCORE 5-10%
Moderate risk	• Grade 2 hypertension • Middle-aged individuals (many of them) • Calculated 10-year SCORE ≥ 1 to < 5%
Low risk	• Calculated 10-year SCORE <1%

SCORE-Systematic COronary Risk Evaluation system; **TOD-**Target organ damage

Source: Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018 Sep 1;39(33):3021-3104.

DBP ≥80 mmHg for prevention of recurrent CV events (secondary CV prevention) and for primary CV prevention in high-risk patients with an estimated ASCVD risk ≥10% and average SBP ≥130 mmHg or average DBP ≥80 mmHg. Also, in patients with diabetes and in those with chronic kidney disease (CKD), pharmacological treatment should be initiated when blood pressure is ≥ 130/80 mmHg. Non-pharmacological treatment should be continued along with drug therapy. These guidelines further recommend that blood pressure treatment goal should be < 130/80 mmHg both in hypertensive patients with known CV disease or 10-year ASCVD risk ≥ 10%; as well as in hypertensive patients without additional markers of increased CV risk.

The European Society of Cardiology (ESC)/European Society of Hypertension (ESH) 2018 guidelines[7] on high blood pressure also recommend prompt initiation of antihypertensive drug therapy along with lifestyle changes in patients with grade 1 hypertension (blood pressure 140-159/90-99 mmHg) and high CV risk or hypertension-mediated organ damage (HMOD), and in those with grade 1 hypertension with low-moderate CV risk and without evidence of HMOD if high blood pressure persists despite a 3-6 months trial of lifestyle changes alone. Pharmacological management for hypertension is also indicated by these guidelines in patients with grade 2 (blood pressure 160-179/100-109 mmHg) or grade 3 hypertension (blood pressure ≥ 180/110 mmHg) irrespective of their CV risk status. They additionally suggest consideration of antihypertensive drug therapy in very high risk patients with high-normal blood pressure (blood pressure 130-139/85-89 mmHg) with comorbid CV disease, especially coronary artery disease (CAD). ESC/EHA recommendations for CV risk stratification are shown in Table 1. The ESC/ESH guidelines also recommend age-based initiation of pharmacological treatment, suggesting it along with lifestyle changes in fit older patients with SBP ≥ 160 mmHg, and also in fit older patients (but not in > 80 years) with SBP in grade 1 hypertension range (140-159 mmHg) provided the treatment is well-tolerated. Treatment objective should be to reduce blood pressure to < 140/90 mmHg, and if treatment is well-tolerated aim to reduce it further to ≤ 130/80 mmHg in most patients. Specifically, in patients < 65 years of age, SBP range of 120-129 mmHg, and in those ≥ 65 years of age, SBP range of 130-139 mmHg should be targeted with close monitoring. A DBP level of < 80 mmHg should be the ultimate treatment objective in most patients.

FRONTLINE ANTIHYPERTENSIVE DRUGS

Diuretics

Diuretics have traditionally been used as front-line antihypertensive therapies. Three groups of diuretics are currently available, thiazides (and thiazide-like diuretics), loop diuretics, and potassium-sparing diuretics.

Hydrochlorothiazide (HCTZ), a typical thiazide, and chlorthalidone and indapamide, two thiazide-like diuretics, have documented role in hypertension management.[3,8] Following a single oral dose, HCTZ achieves peak plasma concentration in about 2 hours and has a half-life of about 6.5 to 9 hours. Chlorthalidone, in contrast, has a longer half-life of about 42 hours (range 29–55 hours). Comparative data demonstrates that 50 mg dose of HCTZ is approximately equivalent to 25–37 mg dose of chlorthalidone.[8] Chlorthalidone is therefore 1.5-2 times as potent as HCTZ, with additional potential for CV risk reduction.[9] Indapamide, another thiazide-like diuretic with a longer half-life than HCTZ, also has antihypertensive properties, additionally appearing better suited than HCTZ to reduce TOD and hypertension-associated complications.[4] It however is apparently underutilized.[9] Indeed, many investigators encourage more frequent use of indapamide, advocating it as the most efficient and tolerable diuretic for hypertensive patients.[10]

Although thiazide diuretics were widely popular antihypertensives in the past owing to their lengthy clinical experience; recently, tolerability issues related to them have emerged, resulting in a decline in their use. Several reports have cited association of thiazides with electrolyte disturbance; and adverse metabolic effects including abnormalities in carbohydrate, lipid, and uric acid metabolism.[9] In particular, dyselectrolytemia is a cause of major concern when prescribing thiazide diuretics.[8] Intriguingly, most of these adverse effects are associated with high doses of diuretics while when used in low doses they are well-tolerated in hypertensive patients, especially the elderly.[9] There were concerns in the past that chlorthalidone and indapamide, owing to their longer half-life than HCTZ, would be more frequently associated with these adverse events, although these have been largely dispelled in recent reports. A recent meta-analysis[8] compared HCTZ with thiazide-like diuretics (chlorthalidone and indapamide) and showed that the latter were associated with greater blood pressure reduction with no greater disturbance of electrolytes or metabolic profile compared to HCTZ. Based on its conceivably better tolerability profile, longer half-life, and proven potential of CV risk reduction, chlorthalidone has currently emerged as the thiazide diuretic of choice upstaging the previously popular HCTZ, although more supporting data in the future will convincingly prove these claims.[3,6]

Loop diuretics are prescribed only in the event of renal diseases, heart failure, and acute pulmonary edema. Potassium-sparing diuretics, such as spironolactone, eplerenone, amiloride and triamterene, are rarely used as front-line antihypertensives but rather reserved for use as adjuncts, especially when their hyperkalemic effects are desirable. They should be used with caution when concomitantly administered with either ACE inhibitors or ARBs due to the risk of clinically significant hyperkalemia.[3]

Beta-blockers

Since their introduction in clinical medicine in 1960s, beta-blockers have remained one of the most popular medications for management of CV disorders. They have been extensively used for managing coronary artery disease (CAD), arrhythmias and heart failure, although their prescription in hypertensive patients is usually reserved for MI, heart failure, and asymptomatic LVH.[3,11,12] Several studies and meta-analyses in the last few years have provided discouraging results, recommending against the use of beta-blockers as first-line therapy for uncomplicated hypertension. One such evaluation[13] of 4 studies that compared atenolol with placebo or no treatment and 5 studies that compared atenolol with other antihypertensive drugs showed similar blood pressure lowering but significantly higher CV mortality and stroke incidence with atenolol compared to other antihypertensive therapies. Similar were results of another large meta-analysis[14] of 7 studies that compared beta-blockers to placebo or no treatment and 13 studies that compared beta-blockers to other antihypertensive drugs, in which relative risk of stroke was 16% higher for beta-blockers compared to other drugs; in the evaluation of placebo-controlled trials, beta-blockers reduced relative risk of stroke by 19%, which was about half that expected from previous hypertension trials. In 2006, results of a landmark meta-analysis[15] were published that re-examined the role of beta-blockers in separate group of younger and older patients with hypertension. Including data of 1,45,811 participants from 21 hypertension trials, results of this meta-analysis showed that beta-blockers compared to placebo reduced major CV outcomes in younger but not older hypertensive patients. Blood pressure lowering efficacy of beta-blockers was comparable to other antihypertensive drugs in younger patients but not in cohort of older patients; besides, in this analysis beta-blockers increased risk of strokes in the elderly. The study investigators therefore recommended against the use of beta-blockers as first-line therapy for uncomplicated hypertension (without other indications of beta-blockers) in elderly patients, although they emphasized its benefits in younger

patients citing significant reduction in CV morbidity and mortality. Although acknowledging the shortcoming of low quality of evidence, a recent Cochrane review[16] reported beta-blockers as inferior to some, though not all antihypertensive agents for specific clinical outcomes. Beta-blockers were inferior to CCBs for total mortality and CV events, and to both CCBs and RAS blockers for strokes. These results have resulted in the demotion of beta-blockers from first- to second- or third-line therapy for uncomplicated hypertension.

It is noteworthy that beta-blockers are a heterogenous class of drugs with varied pharmacological properties. Atenolol was the prototype beta-blocker used in most studies. Third-generation beta-blockers, including nebivolol and carvedilol, differ from their first- and second-generation counterparts primarily in their vasodilatory properties that confer enhanced hemodynamic and metabolic benefits.[12] Blood pressure lowering and metabolic properties of third-generation beta-blockers are especially advantageous when treating hypertension with comorbid diabetes, metabolic syndrome or CAD.[12,17]

Calcium channel blockers (CCBs)

Similar to thiazides and beta-blockers, CCBs are also a widely used class of antihypertensive drugs, with time-tested efficacy in blood pressure lowering, good tolerability, and growing evidence of improved CV outcomes in hypertensive patients.[18] They are categorized into two groups, differing in their structure and relative selectivity towards cardiac vs vascular L–type calcium channels. Dihydropyridines are primarily vasodilators at peripheral vasculature and due to their high vascular selectivity they reduce systemic vascular resistance and arterial pressure. Non-dihydropyridines, on the other hand, act both on cardiac muscles and peripheral vasculature. Dihydropyridines are effective antihypertensives with potential to reduce strokes and CV mortality; non-dihydropyridines are more effectively utilized in arrhythmia management.[3] As per current evidence, compelling indications for use of CCBs include, although are not limited to, management of isolated systolic hypertension in the elderly, hypertension comorbid with metabolic syndrome, LVH or organ damage, previous stroke, or peripheral artery disease. In fact, except for comorbid renal diseases (where RAS blockers should be preferably used), CCBs either as mono- or combination therapy are indicated as first-line therapeutic choice in all stages of hypertension independent of comorbidities.[18]

There is strong data to support reduction of CV events, stroke and mortality with CCBs in hypertensive patients. Results of the ACCOMPLISH trial[19] were a case in the point which confirmed CV risk reduction with a dihydropyridine CCB, especially in combination with an ACE inhibitor. The study recruited 11,506 high-risk hypertensive patients and randomized them to treatment with either a combination of amlodipine (a dihydropyridine) with benazepril (an ACE inhibitor) or amlodipine with HCTZ. The CCB-ACE inhibitor combination was associated with greater reduction in primary study outcomes including a composite of CV deaths, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization compared to ACE inhibitor-HCTZ combination (events rate, 9.6% vs 11.8%, respectively). In effect, CCB-ACE inhibitor combination therapy resulted in an absolute CV risk reduction of 2.2% and relative risk reduction of 19.6%. Recently published results of another meta-analysis[20] confirmed long-term benefits of CCBs in difficult-to-treat, high-risk hypertensive patients such as those with history of CAD or stroke, showing their antihypertensive efficacy to be at least comparable to other first-line blood pressure lowering drugs.

ACE inhibitors

In the pathogenesis of hypertension, RAS is known to play a pivotal role, and therefore blockade of this pathway, with the use of either an ACE inhibitor or ARB, is one of the key therapeutic strategies in hypertension management.[21] ACE inhibitors are specifically recommended as front-line antihypertensive drugs. Being competitive inhibitors of ACE, they block ACE-mediated conversion of angiotensin I to angiotensin II, thereby lowering blood pressure, increasing natriuresis, preventing remodeling of smooth muscles and myocytes, and reducing hydrolysis of the bradykinin to its inactive metabolites; resultant increase in bradykinin contributes to additional vasodilatory action. Although largely well-tolerated, ACE inhibitors have been associated with adverse effects including cough and angioedema.[22] Structural differences among the members of this class account for differences in their pharmacokinetics, potency, affinity for ACE, and toxicity.[23] Since the introduction of the first ACE inhibitor, captopril, these drugs have been widely used and are currently recommended in the management of hypertension, heart failure, CAD, diabetes, and CKD.[24] Their blood pressure-lowering efficacy is similar to other classes of antihypertensive drugs and their efficacy is sustained with long-term treatment.[25]

Several studies[26-28] have evaluated ACE inhibitors across different high-risk patient populations including coronary heart disease (CHD), heart failure and strokes. The SOLVD study[26] showed significant reduction in mortality and incidence of hospitalizations for heart failure, in patients with heart failure and reduced ejection fraction, after addition of enalapril to conventional therapy. The HOPE study[27] also showed significant reduction in mortality, MI, and stroke with the use of ramipril in high-risk patients without evidence of low ejection fraction or heart failure. The EUROPA study[28] showed 20% relative risk reduction in CV events and improved outcomes with perindopril in patients with stable CHD without apparent heart failure. It is noteworthy that these studies included only a proportion of patients with hypertension, and therefore were not truly designed as hypertension trials.

Are ACE inhibitors superior to ARBs?

The role of ACE inhibitors has been compared to ARBs in patients with CV diseases, with or without hypertension. In a large pooled analysis[29] of clinical trials that evaluated efficacy of RAS inhibitors as a group, and separately of ACE inhibitors and ARBs, on all-cause mortality specifically in hypertensive patients, RAS inhibition was shown to be associated with an overall 5% reduction in all-cause mortality, an effect completely driven by ACE inhibitors which were associated with significant 10% reduction in all-cause mortality. In contrast, no clear mortality benefits were seen with ARB treatment. However, the difference in CV mortality between ACE inhibitors and ARBs which was also evaluated in this analysis was not statistically significant. Another large network meta-analysis which compared ACE inhibitors and ARBs,[30] although in patients with diabetes, showed that ACE inhibitors reduced all-cause mortality, CV mortality and major CV events, but not ARBs. However, other recent meta-analyses[31,32] that assessed efficacy of antihypertensive agents on CV outcomes in patients with hypertension or diabetes reported no clear superiority of ACE inhibitors over ARBs. On the contrary, in an analysis[33] of 40,625 patients derived from the Reduction of Atherothrombosis for Continued Health (REACH) registry, which included 91% patients with hypertension (67.9% on ACE inhibitors at baseline and 32.1% on ARBs), ARBs were associated with 10% lower rates of CV events compared with ACE inhibitors, particularly in those with established CV disease.

The current recommendations are to use ACE inhibitors as first-line drugs in CV disease management, indicating the use of ARBs usually as an alternative RAS blocker in ACE inhibitor–intolerant patients. However, these recommendations have been challenged by many investigators as a growing body of evidence shows that these two classes of drugs have little, if any, difference in antihypertensive efficacy with a strong support for superior tolerability of ARBs compared to ACE inhibitors.[24,34]

ARBs

The ARBs have been in clinical use since 1995, and are widely considered effective antihypertensive agents with excellent tolerability profile, both alone and in combination with other blood pressure-lowering agents.[35] In contrast to ACE inhibitors that block conversion of angiotensin I to angiotensin II, ARBs selectively inhibit action of angiotensin II on AT1 receptors, thereby blocking systemic effects of RAS that contribute to hypertension. Additionally, AT1 receptor blockade mediates other benefits including mitigation of inflammation, oxidative stress and remodeling, thereby improving endothelial dysfunction. Moreover, selective AT1 inhibition facilitates angiotensin-driven stimulation of AT2 receptors, hence mediating further natriuresis and vasodilation. Overall, these mechanism confer both CV and renal protection.[24,36] ARBs can be effectively combined with diuretics, CCBs, and beta-blockers, providing incremental blood pressure lowering benefits. Combination of ARBs with their counterpart, ACE inhibitors, although theoretically appealing has not shown any significant benefits, and in fact can increase risk of adverse renal events.[35]

There is growing evidence to show that ARBs confer similar morbidity and mortality reduction benefits beyond their blood pressure lowering effects as ACE inhibitors, with the advantage of a better tolerability profile.[24,34] Within its class, members differ in their lipophilicity, half-lives, receptor-binding affinity, and even blood pressure lowering potential. Also, choice of ARB varies based on the indication it is chosen for.[37]

Several ARBs are currently available. Telmisartan, and to some extent losartan, should be considered in high-risk cases for CV risk reduction; valsartan, candesartan and losartan are preferred in heart failure patients with intolerance to ACE inhibitors; losartan is one of the ARBs of choice for hypertensive patients having increased stroke risk, with additional evidence for telmisartan, candesartan, and eprosartan in this indication; and finally, losartan, valsartan and candesartan should be considered in patients at risk of atrial fibrillations (AF) due to their potential to reduce new-onset AF.[36]

Other novel strategies for hypertension

Despite availability of several treatment options, blood pressure in a proportion of patients remains suboptimally controlled despite use of three or more antihypertensive drugs. Several novel treatment options are being explored to effectively tackle hypertension particularly that which remains uncontrolled on traditional antihypertensive agents.[38] Mineralocorticoid receptor antagonists (MRA) have a well-established role in heart failure management. However, they have also been evaluated in the treatment of resistant hypertension, particularly if caused by aldosterone breakthrough phenomenon; recent results, particularly related to spironolactone, are promising.[39] The PATHWAY-2 trial[40] confirmed effectiveness of add-on spironolactone therapy in treatment-resistant hypertension. The study included hypertensive patients who did not achieve their blood pressure goal despite receiving maximally-tolerated doses of an ACE inhibitor or ARB, CCB and diuretic. In these patients, add-on spironolactone was the most effective antihypertensive therapy, and when added to previous treatment regimen achieved greater home SBP reduction compared to placebo, doxazosin and bisoprolol. Another novel treatment approach being pursued for managing difficult-to-treat hypertension is dual angiotensin II-neprilysin inhibitor (ARNI). The first member of this class, valsartan and sacubitril combination (LCZ696), was recently evaluated in patients with mild-to-moderate hypertension and showed greater blood pressure reduction than valsartan alone. More data however is required to attest this claim. Moreover, LCZ696 was well-tolerated with no reported case of angioedema.[41] Overactivity of the brain RAS along with angiotensin II and angiotensin III, its two bioactive peptides, have also been implicated in development of hypertension. Aminopeptidase A converts angiotensin II to angiotensin III; and therefore its inhibition is suggested as a promising treatment strategy in hypertension management. These findings are still early and require supporting evidence to attest their veracity.[38] Research is ongoing and several new antihypertensive agents will be added to the treatment armamentarium in the near future, thereby providing clinicians more viable treatment options to choose from.

CONCLUSION

Hypertension is currently an emerging public health challenge with serious ramifications. It contributes to CV events, TOD, high morbidity and mortality rates. Its early diagnosis and timely blood pressure control is the key to reduce burden of target-organ complications. Lifestyle modifications remain the first-line treatment approach for hypertension; however, a significant proportion of patients eventually require pharmacological treatment to reduce blood pressure to goal. Front-line antihypertensive drug classes include diuretics, RAS inhibitors including ACE inhibitors and ARBs, beta-blockers, and CCBs. However, despite their use, blood pressure in a percentage of patients remains poorly controlled; for which several novel treatment strategies are being evaluated and are likely to be included in the antihypertensive treatment armamentarium in the near future.

TAKE HOME POINTS

- While initial approach to management of hypertension should involve lifestyle changes, particularly stress control, physical exercises and weight management, eventually pharmacological management is required if lifestyle changes alone remain inadequate in reducing blood pressure to goal
- Thiazide diuretics were widely popular antihypertensives in the past owing to their lengthy clinical experience; however, recently tolerability issues related to them have emerged, resulting in a decline in their use
- Third-generation beta-blockers, including nebivolol and carvedilol, differ from their first- and second-generation counterparts primarily in their vasodilatory properties that confer enhanced hemodynamic and metabolic benefits
- A growing body of evidence shows that ACE inhibitors and ARBs have little, if any, difference in antihypertensive efficacy with a strong support for superior tolerability of ARBs compared to ACE inhibitors.

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Usual dosages and frequency of common oral antihypertensive drugs			
Class	**Drug**	**Usual dose, range**	**Frequency**
Thiazide or thiazide-like diuretics			
	Chlorthalidone	12.5–25 mg/day	Once daily
	Hydrochlorothiazide	25–50 mg/day	Once daily
	Indapamide	1.25–2.5 mg/day	Once daily
	Metolazone	2.5–5 mg/day	Once daily
ARBs			
	Azilsartan	40–80 mg/day	Once daily
	Candesartan	8–32 mg/day	Once daily
	Telmisartan	20–80 mg/day	Once daily
	Olmesartan	20–40 mg/day	Once daily
	Irbesartan	150–300 mg/day	Once daily
	Valsartan	80–320 mg/day	Once daily
	Losartan	50–100 mg/day	Once/twice daily
	Eprosartan	600–800 mg/day	Once/twice daily
ACE Inhibitors			
	Captopril	12.5–150 mg/day	Twice/thrice daily
	Enalapril	5–40 mg/day	Once/twice daily
	Ramipril	2.5–20 mg/day	Once/twice daily
	Benazepril	10–40 mg/day	Once/twice daily
	Lisinopril	10–40 mg/day	Once daily
	Fosinopril	10–40 mg/day	Once daily
	Perindopril	4–16 mg/day	Once daily
	Moexipril	7.5–30 mg/day	Once/twice daily
	Quinapril	10–80 mg/day	Once/twice daily
	Trandolapril	1–4 mg/day	Once daily
CCB (Dihydropyridines)			
	Amlodipine	2.5–10 mg/day	Once daily
	Felodipine	2.5–10 mg/day	Once daily
	Nifedipine LA	30–90 mg/day	Once daily
	Nicardipine SR	60–120 mg/day	Twice daily
	Nisoldipine	17–34 mg/day	Once daily
	Isradipine	5–10 mg/day	Twice daily
CCB (Non-dihydropyridines)			
	Diltiazem ER	120–360 mg/day	Once daily
	Verapamil SR	120–360 mg/day	Once/twice daily
	Verapamil IR	120–360 mg/day	Thrice daily
	Verapamil-delayed onset ER	100–300 mg/day	Once daily (in the evening)

Source: Whelton PK, et al. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 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. *Hypertension*. 2017;00:e000-e000.

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