24-Hour Blood Pressure Control with Amlodipine: A Review of the Current Scenario

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Abstract

Introduction Hypertension is the leading cause of cardiovascular diseases and premature death worldwide. Antihypertensive therapy using calcium channel blockers (CCBs) is one of the preferred choices to treat blood pressure (BP) and control blood pressure variability (BPV). In contrast to clinic BP, 24-hour ambulatory BP monitoring (ABPM) has evolved into an accurate and reproducible tool for the assessment and management of hypertension. Amlodipine, a longer acting dihydropyridine CCB is effective for 24 hours BP control and also minimizing BPV. The present article is the comprehensive review highlighting the efficacy of amlodipine in controlling 24-hour BP and minimizing BPV from the review of recent studies.

Materials and Methods The literature search was done using PubMed, Google Scholar, and MEDLINE databases. The studies to be included for review, were identified through the keywords: "amlodipine," "ambulatory BP monitoring (ABPM)," "blood pressure variability (BPV)," "CCBs," and filtering articles published in English language only.

Results Pharmacological evidence suggests that amlodipine has the ability to block all the subtypes of CCBs such as L-, N-, P-, Q-, R-, and T-type. Various clinical studies reported that amlodipine is a powerful, well-tolerated, and safe antihypertensive agent which is widely used either alone or as a key component of combination therapy for control of 24 hours BP.

Conclusion Overall, amlodipine is a proven and effective antihypertensive drug and helpful in controlling 24-hour BP, minimizing BP variability and hence reducing the risk of cardiovascular complications.

Keywords
► hypertension
► amlodipine
► calcium channel blockers

Introduction

Hypertension is an important worldwide public-health challenge, often referred to as "the silent killer" owing to it being a major risk for myocardial infarction (MI) and the most important risk factor for stroke.[1] Globally, high systolic blood pressure (SBP) is the leading risk factor accounting for 10.4 million deaths and 218 million disability-adjusted life-years (DALYs).[2]

The World Health Organization (WHO) estimates that of 1.13 billion people with hypertension worldwide, two-thirds are in low and middle income countries (LMICs) and this number is expected to increase over 1.56 billion by 2025. A systematic review and meta-analysis of 242 studies reported that in LMICs, one in three persons had hypertension (mean age: 45.9 ± 12.1 years).[3] In India, hypertension is a significant public health problem. A recent national level survey conducted across 24 states and union territories of India reported an overall prevalence of 30.7% in adults, implying that almost one in three participants has hypertension.[4] However, only less than one in five people with hypertension have the blood pressure (BP) under control.[5,6] An important reason for poor BP control may be late or ineffective treatment that could lead to irreversible or difficult to reverse adaptations of the cardiovascular (CV) system.[7] Trials like Valsartan Antihypertensive Long term Use Evaluation (VALUE), the Study on Cognition and Prognosis in the Elderly (SCOPE), and the Systolic Hypertension in Europe (Syst-Eur) trials suggested the importance of early and 24-hour control of BP with regards to CV outcome (►**Fig. 1**).[8]

It has been long recognized that BP varies as per circadian rhythm, dipping at night during rest, increasing steeply in the morning (known as the "morning surge"), and peaking typically in the late afternoon.[9] Thus, measurement of blood pressure variability (BPV) over a period of 24 hours (outside clinic) is recommended. The 24-hour readings obtained during the patient's daily activities provide a precise assessment of the true BP. The main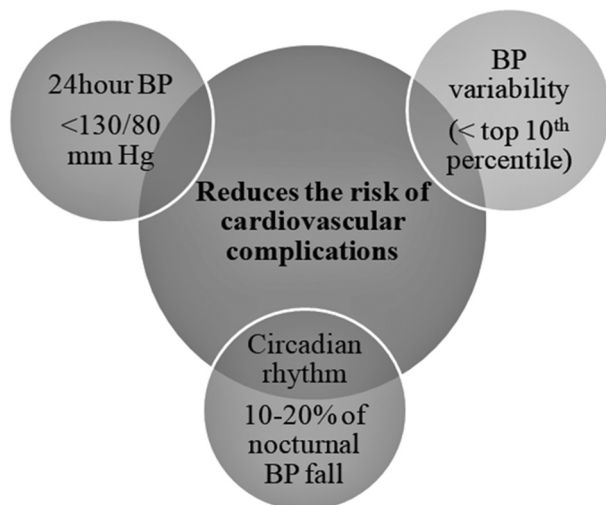 prognostic features of 24-hour BP measurement are daytime ambulatory systolic/diastolic BP, night time ambulatory SBP, night time ambulatory diastolic BP, ambulatory pulse pressure, and presence or absence of nocturnal dip. Ambulatory blood pressure monitoring (ABPM) is now considered better in diagnosing hypertension outside of a clinic environment[10–12] as BP is measured at daytime and night time at different intervals. Majorly, ABPM includes repeated measurement of BP at predetermined intervals ranging from 10 to 60 minutes during the day and night time. A previously published study concluded that ABPM gave the most accurate measurement of BP in comparison to home or clinical measurements.[13]

Further, ABPM can measure the BPV and eliminates observer bias.

Recent studies also suggested shortcomings in the measurement of office BP related to device, observer, and patient-related factors. White coat hypertension is a commonly encountered phenomenon wherein, a higher BP reading is observed at doctor's office. Masked hypertension and nocturnal hypertension are also not diagnosed with office BP.[14] Based on these observations, the hypertension guidelines are continually evolving, translating new knowledge to clinical practice.[15] Earlier, the guidelines were more focused on absolute decrease in SBP/DBP but a paradigm shift to monitor 24-hour BP obtained during the patient's daily activities for a precise assessment of the true BP was incorporated in all the hypertension guidelines.[16] Further, ABPM has been recognized as a better predictor of clinical outcomes in numerous studies.[17–19] A study conducted in 1,007 subjects showed that 24-hour daytime and night time AMBPs were closely associated with the risk of silent cerebrovascular lesions detected by brain magnetic resonance imaging, whereas the clinic BP values were not associated with subclinical cerebrovascular events.[20] The Syst-Eur Trial sub-study also noted that in elderly subjects with untreated isolated systolic HTN, ABPM was a significant predictor of CV risk.[21] A systematic review of 20 studies concluded that ABPM gave the most accurate measurement of BP in comparison to home or clinic measurements.[22] The threshold values for ABPM in guidelines NICE, JNC-8, ESH/ESC/ are summarized in ►**Table 1**.

A substantial number of studies advocated that BPV (ultrashort term, short term and long term) is a causative factor for different CV diseases like left ventricular hypertrophy (LVH) that further leads to organ damage.[23] BPV or the fluctuation in the BP is complex and includes both the short-term (within minutes to hours) and long-term variations (includes days and months); the latter being more reliable than former on the grounds that it is better predictor of the CV outcomes.[24] Accordingly, CV protection by antihypertensive treatment should aim not only at achieving control of the average BP values, but also at stabilizing BPV. The ability of ABPM to provide a quantification of BP throughout the 24-hour period during an individual's normal daily routine is one of the reasons for its high prognostic value.

To avoid the risk of CV complications, it is crucial that the 24-hour BPV is controlled. Thus, an antihypertensive drug

Fig. 1 Relation between 24-hour BP control and cardiovascular complications.

Table 1 Different recommendations for diagnosis of hypertension

Organization, year	Indications	Diagnostic protocol and threshold	Ambulatory blood pressure monitoring, mm Hg
American Society of Hypertension, 2014[55]	Hypertension, white-coat hypertension	Diagnosis confirmed: at an additional patient visit, usually 1–4 wk after the first measurements. OBPM diagnostic threshold: ≥140/90 mm Hg HBPM diagnostic threshold: ≥135/85 mm Hg	ABPM is another approach if available.
Joint National Committee on Prevention, Detection, Evaluation and Treatment of Blood Pressure (JNC 7), 2004[56]	Suspected white-coat hypertension among hypertensive patients and no target organ damage; hypotensive symptoms with antihypertensive medication	Stage 1 hypertension diagnosis should be confirmed within 2 mo after initial elevated OBPM (no further protocol details reported). Stage 2 hypertension should be confirmed within 1 mo; those with ≥180/110 mm Hg evaluate and treat immediately.	ABPM diagnostic threshold: ≥135/85 (awake), ≥120/75 (asleep)
National Institute for Health and Care Excellence, 2011[57]	Hypertension, white-coat hypertension	Adults aged 18–21 y only. Based on repeated measures in both arms followed by ABPM (at least 14 measurements) or HBPM (twice in morning and evening for at least 4 d, ideally 7 d) if ABPM not tolerable. OBPM diagnostic threshold: ≥140/90 mm Hg	ABPM diagnostic threshold: ≥135/85 (daytime)
National Heart, Lung, and Blood Institute, 2013[58]	Hypertension, white-coat hypertension	Based on two OBPM measurements, confirm elevated reading with contralateral arm.	
University of Michigan Health System, 2009[55]	Hypertension, white-coat and masked hypertension	Based on taking mean blood pressure levels from recordings over several visits. Suspected white-coat hypertension: three or more OBPM >140/90 mm Hg	ABPM <140/90
Canadian Hypertension Education Program (CHEP), 2013[59]	Hypertension, suspected white-coat hypertension, and masked hypertension	OBPM diagnostic threshold: ≥160/110 mm Hg averaged across three visits; or if ≥140/90 mm Hg averaged across five visits	ABPM diagnostic threshold: ≥135/85 (awake) or ≥130/80 (24 hours) HBPM diagnostic threshold: ≥135/85
European Society of Hypertension, 2008[60]	Sustained, masked or white-coat hypertension	HBPM diagnostic threshold: 135/85 mm Hg	ABPM diagnostic threshold: ≥135/85 (awake), ≥120/70 (asleep) and ≥130/80 (24 h)
Institute for Clinical Systems Improvement, 2012[61]	Confirming initial elevated BP; white-coat or masked hypertension	Based on a combination of one or more follow-up visits with at least two blood pressure readings at each visit and an out-of-office blood pressure measurement (e.g., HBPM) or 24 h ABPM.	ABPM diagnostic threshold: 140/85 (awake), 120/70 (asleep), and 130/80 (24 h)
HOPE ASIA 2020 Guidelines		ABPM: gold standard for diagnosing and monitoring of hypertension	Diagnostic thresholds for hypertension using ABPM are as follows: average 24-h BP of ≥130/80 mm Hg; average daytime BP of ≥135/85 mm Hg
ISH 2020 Guidelines	Confirming initial elevated BP; white-coat or masked hypertension		ABPM: 24-h average ≥130 and/or ≥80, Day time (or awake) average ≥135 and/or ≥85, Night time (or asleep) average ≥120 and/or ≥70, HBPM ≥135 and/or ≥85
Japanese Society of Hypertension, 2009[62]		Based on blood pressures measured on at least two different clinic-based	

(*Continued*)

Table 1 (Continued)

Organization, year	Indications	Diagnostic protocol and threshold	Ambulatory blood pressure monitoring, mm Hg
	Diagnosis of essential, white-coat, and masked hypertension	occasions. OBPM diagnostic threshold: ≥140/90 mm Hg HBPM diagnostic threshold: ≥135/85 mm Hg	ABPM diagnostic threshold: ≥130/80 (24 hour), ≥135/85 (day), ≥120/70 (night)

Comparison of National recommendations for Ambulatory BP (Clinic BP = 140/90 mm Hg)			
Guideline	**Ambulatory BP monitoring mm Hg**		
	24 h	**Night**	**Day**
Seventh Joint National Committee (USA, 2003)[63]	Not stated	120/75	135/85
European Society of Hypertension (2013)[64]	130/80	120/70	135/85
Japanese Circulation Society (2012)[65]	130/80	120/70	135/85
Canadian Hypertension Society (1999)[66]	130/80	120/75	135/85
Australian National Heart Foundation and High BP Research Council Consensus (2012)[67]	130/80	120/75	135/85
National Institute for Health and Clinical Excellence (UK, 2011)[40]	Not stated	Not stated	135/85

Abbreviations: HBPM, home blood pressure monitoring; NR, not reported; OBPM, office blood pressure measurement.

with low BPV and a high smoothness index (SI) is a pragmatic approach. SI provides a useful measure of antihypertensive treatment efficacy over the 24-hour dosing period, its values being highest with antihypertensive agents that have large and consistent effects across 24 hours. A large SI usually indicates a consistent average BP reduction associated with a small variability among hours, and thus a superior CV protection and an improved prevention of target-organ damage.[25] An ideal anti-hypertensive therapy, thus, has a multi-modal approach; it should have a longer half-life, should be able to control BP over a period of 24 hours, should be able to reduce BPV, and should have a higher SI.

Amlodipine for the Management of Hypertension

All the major hypertensive guidelines recommend calcium channel blockers (CCBs) as one of the first line antihypertensive drugs. Trials like ALLHAT, VALUE, ASCOT, and ACCOMPLISH recommend CCB-based therapy for the management of normal and high CV risk hypertensive patients.

Amlodipine, a long-acting, lipophilic, third generation dihydropyridine (DHP) CCB has demonstrated a strong evidence of safety and efficacy in BP and CV event reduction in large randomized controlled trials. The outcomes of these trials are summarized in ►**Table 2**. The WHO has mentioned amlodipine in its list of essential medicines and it is denoted as the safest and most effective medicine required in health system.[13]

Amlodipine: Blocks All Types of Calcium Channels

Broadly, CCBs reduce the influx of calcium ions into the vascular and cardiac smooth muscle cells which help in pumping of blood smoothly by heart. Calcium channels (Ca^{2+}) are broadly classified into at least six subtypes; namely, L-, N-, P-, Q-, R-, and T-type, based on electrophysiological and pharmacological evidence. L-type of voltage-gated CCBs are used as a first or second line drug in the management of hypertension as they are potent vasodilators. Amlodipine confers the pharmacological action by inhibiting the voltage-gated calcium ion channel (Ca_V).[26] The L-type calcium channel is inhibited by amlodipine that prevents the influx of calcium ions into the transmembrane of cardiac and vascular smooth muscle cell.[27] Amlodipine is not only an L-type but also an N-type

Table 2 Evaluation of clinical trials conducted with amlodipine

Trial (Experiment vs. control)	No of patients	Follow up (Years)	Outcome of interest (No of events)			Survival analysis [(OD/HR/RR) 95% CI]		
			Fatal CHD/MI	Stroke	All-cause mortality	CHD	Stroke	All-cause mortality
VART[c] (Amlodipine vs. Valsartan)	Amlodipine:316	3.4	1	7	2	1.04 (0.07–16.5)	1.18 (0.43–3.23)	0.69 (0.12–4.1)
	Valsartan: 305		1	8	3			
ALLHAT[a] (Amlodipine vs. Lisinopril)	Amlodipine: 9,048	4.9	798	377	1256	1.01 (0.91–1.11)	1.05 (0.97–1.13)	1.23 (1.08–1.41)
	Lisinopril: 9,054		796	457	1354			
CAMELOT[b] (Amlodipine vs. Enalapril)	Amlodipine: 673	2	110	6	7	0.69 (0.54–0.88)	0.50 (0.19–1.32)	0.92 (0.33–2.52)
	Enalapril: 663		136	12	6			
ASCOT (Amlodipine vs. Atenolol)	Amlodipine: 2,565	5.5	93	18	245	0.89 (0.67–1.17)	0.82 (0.44–1.52)	0.98 (0.82–1.17)
	Atenolol: 2,572		105	22	250			
VALUE[c] (Amlodipine vs. Valsartan)	Amlodipine: 7,596	4.2	313	281	818	1.19 (1.02–1.38)	1.15 (0.98–1.35)	1.04 (0.94–1.14)
	Valsartan: 7,649		369	322	841			

Abbreviations: ALLHAT, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes; CAMELOT, The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; OD, odds ratio; RR, relative risk; VALUE, The Valsartan Antihypertensive Long-term Use Evaluation; VART; Valsartan Amlodipine Randomized Trial.
[a]Odds ratio is the survival analysis in the study.
[b]Relative risk is the survival analysis in the study.
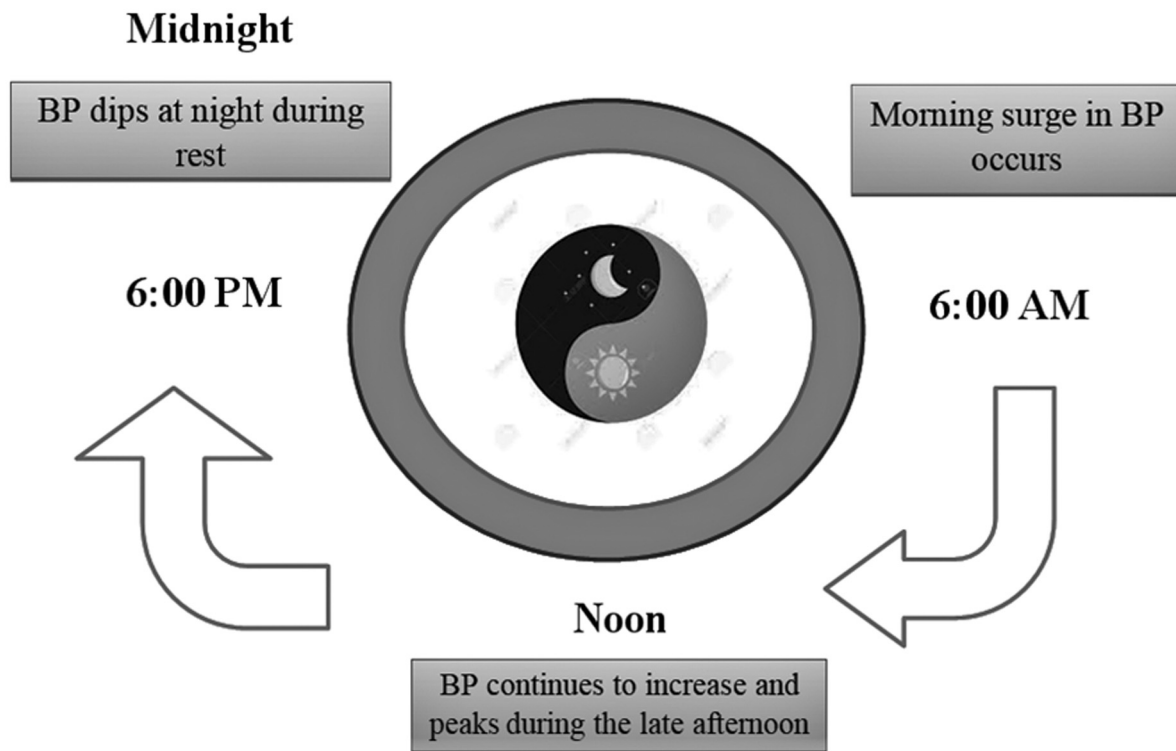[c]MI is the outcome of interest.

Fig. 2 Circadian rhythm

and P/Q-type CCBs as published studies reported that amlodipine blocks N-type Ca^{2+} and P/Q-type channels as well. Furthermore, the kinetic interaction of amlodipine shows a very slow rate of association and dissociation from its binding sites that lead to a gradual onset of action (►**Fig. 2**).[28]

Pharmacological Actions Evidencing Clinical Efficacy

The elimination of amlodipine from the plasma is biphasic and the termination half-life is approximately 30 to 50 hours. The renal route is the preferred route of excretion of metabolites of amlodipine; however, a part (20–25%) is also excreted via biliary route.

Effect on Blood Pressure and Other Hemodynamic Effects

A summary of all the clinical studies targeting the efficacy of amlodipine in reducing BP is represented in ►Table 3. Amlodipine at a mean dose of 10 mg effectively controlled BP throughout the 24 hours both at rest and during the exercise by lowering the total peripheral resistance without lowering the cardiac output.[29]

Evidence of 24 Hours BP Control by Amlodipine

Compared with nifedipine and other medications in the DHP class, amlodipine has the longest half-life at 30 to 50 hours; longer half-life confers it the ability to have once daily dosing (►Table 4).

Amlodipine shows a gradual and prolonged reduction in BP due to its longest elimination half-life and slow receptor dissociation kinetics. Zhang et al conducted a X-CELLENT trial with 577 patients and reported that amlodipine was efficacious and tolerable across all timeframes even after adjustment for mean BP reduction as it significantly decreased daytime, night time and 24-hour SBP variability; whereas indapamide significantly decreased SBP variability in the daytime and 24 hours.[30] The Circadian Anti-Ischemia Program in Europe (CAPE), a large, 10-week international (63 sites), double-blind, parallel study conducted with 1160 patients reported that amlodipine significantly reduced both symptomatic and asymptomatic ischemic events over 24 hours in patients with chronic stable angina.[31] Another pooled analysis of five different studies reported that BPV with amlodipine was significantly (p <0.0001) lower compared with atenolol, lisinopril, and enalapril.[32] A randomized trial reported that amlodipine 5 mg once daily, was well tolerated and effective in maintaining both DBP and SBP below the baseline levels at every hour during the 24-hour observation period.[33] A comparative analysis of valsartan and hydrochlorothiazide and amlodipine reported that amlodipine was as effective as valsartan and hydrochlorothiazide in controlling the 24-hour BP as well as night time and daytime BP levels from baseline.[34]

A considerable number of studies estimated the efficacy of amlodipine on ABPM through a reliable parameter; SI whose higher value indicates a better antihypertensive effect. SI is calculated as the ratio between the average of the 24 hourly BP changes induced by a given medication and the standard deviation of hourly reductions and it represents the useful measures of the homogeneity of the antihypertensive effect over 24 hours; in fact the SI provides a superior measure of the homogeneity of BP.[35] All combination therapies have higher SI than monotherapy. Amlodipine is consistent in BP reduction throughout 24 hours because of a high trough to peak concentration (T: p = 0.85) and a high SI. The 24-hour SI

value for amlodipine 5 mg was higher than those of manidipine, lercanidipine, nifedipine, felodipine, and diltiazem.[25] A meta-analysis of 11 randomized studies encompassing 5,188 hypertensive patients that investigated the SI of losartan, valsartan, telmisartan, ramipril, and amlodipine, reported that amlodipine 5 mg had higher SI than any other anti-hypertensive agent. In the same study, amlodipine 5 mg was found to have a higher SI than lercanidipine and manidipine in the patients with mild to moderate hypertension.[36] Amongst spirapril and amlodipine, SI of amlodipine (0.65/0.45) was reported to be higher (spirapril: 0.55/0.45) implying high advantages for amlodipine in the long-term treatment.[37] Cho et al in their 20-week study reported that 24-hour ambulatory central BP was well controlled in losartan/amlodipine (−9.7 ± 10.67 mm Hg) group as compared with losartan/HCZ (−6.28 ± 10.50 mm Hg) group. Moreover, the pulse pressure was also significantly reduced in the amlodipine (45.4 ± 8.1 mm Hg) group than that (48 ± 8.3 mm Hg) in the HCZ group.[38] Huang et al reported that amlodipine was more efficacious (2–3 mm Hg) than nifedipine in reducing the 24-hour BP when the dose of medication got missed.[39] A phase IV study investigated the effect of amlodipine/valsartan on the mean 24-hour ambulatory BP when given in the morning (6–10 AM) and evening (6–10 PM). Following 4 weeks of treatment, the patients who took dose in morning, and evening showed a mean reduction of −12.16 (0.88)/− 11.17 (0.90) mm Hg in SBP, respectively while the reduction of DBP in morning, and evening was −7.71 (0.59) and −7.01 (0.60) mm Hg, respectively.[40] A study reported that amlodipine in combination with either perindopril or HCZ was more effective at reducing ABPM as compared with the FDC of HCZ/perindopril in Black African patients. The mean difference in 24-hour SBP between baseline and following 6 months of amlodipine/HCZ and amlodipine/perindopril therapy was −3.14 and −3 mm Hg, respectively that were comparable to the mean reduction of −2.59 mm Hg in HCZ/perindopril group.[41]

Outcome Benefits of Amlodipine in Cardiovascular Diseases and Renal Failure

LVH generally develops in response to hypertension and causes left ventricle to work harder.[42] Antihypertensive drugs are known to lower the risk of LVH by maintaining the BP within range. Long-acting CCB administration is helpful in maintaining the serial changes in left ventricular (LV) function and morphology in hypertensive patients with LV hypertrophy. A study of 32 hypertensive patients demonstrated that administration of 5 mg amlodipine/d resulted in a significant decrease in SBP within 1 month and a significant reduction in septal thickness and LV mass index at 6 and 12 months.[17] Yilmaz et al in a study with 112 hemodialysis patients observed that LV mass index decreased in subjects with concentric LVH after administration of amlodipine.[18] Another study conducted by Adalet et al also reported similar results in 19 patients with hypertension; amlodipine was effective in lowering the BP and reduced the risk for LVH in all the patients.[43]

Table 3 Clinical studies conferring the efficacy of amlodipine in hypertension

Primary citation of study	Design of study	Dose[a]	Study duration	Primary end point of interest	Result[b]
Silke et al[68]	Treatment versus no treatment control group	20 mg (IV) amlodipine	Immediate dose response was measured	Mean reduction in SBP and DBP	Control (SBP/DBP): 145 ± 5/130 ± 4 mm Hg; Treatment (SBP/DBP): 80 ± 2/72 ± 2 mm Hg
Lund-Johansen et al[29]	Placebo-controlled	Amlodipine 5 mg initially and 10 mg (if necessary)	11 mo	Mean reduction in BP at rest (sitting) and after work (sitting)	Rest: Placebo group; 182 ± 16.1 (SBP)/111.2 ± 8.1 mm Hg (DBP); After treatment at rest; 153.4 ± 10.7/95.6 ± 5.7 mm Hg (SBP/DBP) After work (without treatment); 204 ± 12.9/112.7 ± 8.1 mm Hg; After treatment: 176.9 ± 15.5 (SBP)/96.9 ± 7.9 (DBP) mm Hg
Broadhurst et al[69]	Placebo-controlled	5 mg (2 wk) amlodipine initially and thereafter 10 mg (4 wk)	6 wk	Reduction in mean supine cuff BP	Placebo group: 169/104 mm Hg Treatment group: 146/92 mm Hg
Burris et al[33]	Double-blind, randomized placebo-controlled, and single-site	5 mg amlodipine	4 wk	Mean reduction in supine BP from baseline	Baseline (SBP/DBP) to final (SBP/DBP); Placebo: 146.9/100 to 154 mm Hg/97.3 mm Hg; Treatment: 156/99.3 to 138/86.3 mm Hg
Sharma et al[41]	Comparative, phase-3, multicenter, and prospective	5 mg (amlodipine), and telmisartan 40 mg + amlodipine 5 mg (FDC)	12 wk	Reduction in SBP and DBP	SBP: A [16.6%], (T+A [−27.4%]; DBP: (T+A [20.1%]; A [−13.3%]) (all, $p < 0.05$)
Bahl et al[70]	Prospective and multicenter	FDC (perindopril; 4 mg and amlodipine 5 mg)	60 d	Mean change in BP from baseline	−41.9 ± 34.8 (SBP)/−23.2 ± 21.8 (DBP) mm Hg; $p < 0.0001$) from baseline (167.4 ± 15.2/101.4 ± 9.1 mm Hg)
El-Etriby et al[71]	Multicenter, open label, prospective, and cohort	SPC: Aml/Val/HCTZ; 10/160/25 mg or 5/160/12.5 mg	12 wk	Mean change in BP from baseline	165.5 ± 12.83/100.8 ± 7.03 mm Hg from baseline (129.7 ± 8.35/80.6 ± 5.25 mm Hg); ($p < 0.0001$)
Dharapurand Patil[72]	Parallel group, open label, prospective, and comparative	Amlodipine (5–10 mg)	8 wk	Mean change in BP from baseline	SBP: 132.72 ± 4.91 mm Hg; DBP: 82 ± 2.55 from baseline (151.56 ± 10.21/95.4 ± 5.70 mm Hg)
Nwachukwu et al[73]	Single-blind randomized	Amlodipine 5 mg	4 wk	Reduction in SBP and DBP	SBP: −17.69 ± 3.12 mm Hg; DBP: −12.36 ± 2.40 mm Hg

Abbreviations: Aml, amlodipine; BP, blood pressure; DBP, diastolic blood pressure; FDC, fixed dose combination; HCTZ, hydrochlorothiazide; IV, intravenous; SBP, systolic blood pressure; SPC, single pill combination; Val, valsartan.

[a]All the doses are once in a day except the first study.

[b]Results are expressed as mean ± standard deviation except the first study; mean ± standard error.

Some major trials reported promising effects of amlodipine on varied CV diseases. Prospective Randomized Amlodipine Survival Evaluation Study Group (PRAISE) reported that amlodipine improved the morbidity and mortality in the patients with non-ischemic cardiomyopathy, but not the ones with ischemic heart diseases.[44] In the PREVENT study, amlodipine retarded the progress of coronary atherosclerosis, and incidence of CV events was not increased.[45] The VALUE study demonstrated that there is no difference in the incidence of heart failure or stroke between amlodipine- and valsartan-treated patients, in fact the incidence of MI was rather lower in amlodipine-treated group.[46] Amlodipine is also demonstrated to reduce CV events compared with enalapril and placebo in the CAMELOT study.[47]

Another public health problem associated with hypertension is altered urinary albumin creatinine ratio which is an early sign of kidney damage. Microalbuminuria in hypertensive patients is associated with increased mortality and it is an independent risk factor for CV and cerebrovascular complications.[5] A randomized trial conducted with 72 patients with hypertension and type 2 diabetes mellitus reported that CCBs can help in the reduction of microalbuminuria as CCBs dilate afferent arterioles and possibly increase intraglomerular pressure. They found that anti-albuminuric effect of cilnidipine is similar to anti-albuminuric effect of amlodipine.[48]

Effect on Kidney

The beneficial pharmacological effects of amlodipine on kidney have been very well documented in preclinical and clinical studies and discussing all of them will be out of scope of this review. An interesting fact about these studies is that they advocate the counteracting effect conferred by amlodipine on the norepinephrine, angiotensin II, and dilatation of afferent and efferent arteriole that are increased in the patient with hypertension. Amlodipine was reported to lower the mean arterial pressure along with the increase in the value of p-aminohippurate clearance (19%), inulin clearance (13%), and a decrease in renal vascular resistance (25%) in the patients with hypertension.[49] In a 1 year study comparing amlodipine with enalapril, an annual decline in creatinine clearance was reported to be −3.7 mL/min/y and −2.6 mL/min/y in amlodipine and enalapril group, respectively in hypertensive patients with renal abnormalities.[50]

Cost-Effectiveness of Amlodipine-Based Treatment Regimen

The cost of antihypertensive drugs imposes a huge burden on patients. A study conducted by Chan et al reported that amlodipine-based treatment regimen has not only better effectiveness but is also predicted to be cost saving when compared with valsartan.[51] Studies conducted in Europe, North America, and China showed that amlodipine was associated with improved clinical outcomes and lower total cost compared with traditional treatments for hypertension or coronary artery disease.[52,53]

In India, cost effectiveness analysis of antihypertensive drugs reported atenolol to be the most cost-effective drug (INR 5.5/unit of effectiveness), followed by the amlodipine and losartan combination (INR 5.6) and amlodipine (INR 6.3).[54]

Conclusion

Amlodipine is a trusted and well-tested CCB that blocks all the subtypes of calcium channels, effectively controls BP while maintaining circadian rhythm and reduces the risk of CV and cerebrovascular complications. Amlodipine is an excellent first line choice among all the other antihypertensive agents. The efficacy and safety of amlodipine are extensively studied and well established as a monotherapy as well as a combination therapy. Amlodipine with an effective BP control over 24 hours and low BPV reduces the progression of severe complications. Its longer half-life and higher SI lead to a consistent average BP reduction. Amlodipine is a trusted and cost-effective option not only for controlling BP but also for safely improving patient outcomes.

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