REVIEW ARTICLE

Amlodipine in the Era of New Generation Calcium Channel Blockers

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Abstract

Amlodipine is a classical drug with varied properties extending from control of blood pressure to as an antianginal and anti atherosclerotic agent. Amlodipine is a longer acting dihydropyridine calcium channel blocker, effective for 24 hours BP control and cause no BP variability. It is a powerful, well-tolerated, and safe antihypertensive agents that is widely used either alone or as a key component of combination therapy for hypertension. Its effective BP reduction has shown proven benefits in cardiovascular event reduction that is supported with strong evidences from large randomised controlled trials. Combination therapies of amlodipine with other agents eliciting renin-angiotensin-aldosterone system blockade (angiotensin II receptor blockers or renin inhibitors) have shown effective blood pressure-lowering strategies in CV risk reduction and progression of renal disease. Novel type of calcium channel blockers have been developed which have additional properties of blocking T and N subtypes of calcium channels and apart from their class effects they exerts specific action on heart rate and renin aldosterone system. They are considered to be more renoprotective due to this additional properties. Amlodipine is most potent and longer acting agent compared to the newer CCBs, its effectiveness in BP lowering still makes it the agent of choice among all the CCBs.

Hypertension a universal public health hazard, a leading cause of mortality and ranked third as a cause for disability -adjusted life years.[1] It affects approximately 26% of the population worldwide, nearly 45% of deaths by heart disease and 51% of deaths by stroke are due to hypertension; accounting for 9.4 million deaths worldwide every year.[2,3] In India, its prevalence varies from 20-40% in urban to 12-17% in rural areas. It is estimated that the prevalence of hypertension(HTN) might rise to 214 million by 2025.[4] For the management of hypertension various classes of antihypertensive drugs are available such as diuretics, β-blockers (BB), α blockers, calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs),that can be used as monotherapy or in combination.[5] Dihydropyridine calcium channel blockers are a class of powerful, well-tolerated, and safe drugs widely used is in the management of elevated blood pressure (BP) as a monotherapy or as a key component of combination therapy for hypertension. The initial indication, besides hypertension, also include angina and peripheral vascular disease.[6,7] Amlodipine was introduced in early 90's' has many unique qualities that set it apart from other agents in this class. It is a third generation Dihydropyridine (DHP) calcium antagonist, with high selectivity for vascular smooth muscle, has minimal impact upon heart rate, and no negative inotropic effects or electrophysiological disturbances.[8] It is an extensively studied classical drug with varied properties extending from control of blood pressure to as an antianginal and anti atherosclerotic agent. The newer generation DHPs block L/N type calcium channel of which cilnidipine is considered more renoprotective. Amlodipine, despite of the new generation CCBs, it still remains one of the top global pharmaceutical products. Its effectiveness in lowering blood pressure in addition to high tolerability and minimal side effects has made it an agent of choice in both single and combination drug treatment for reducing the burden of cardiovascular disease across the globe.[9] The aim of the review is to assess the potential advantages of amlodipine above the new DHPs with a focus of its benefits in varied cardio vascular diseases.

Pharmacodynamics and Pharmacokinetics

Calcium channels(Ca^{2+})are 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 calcium channel blockers (CCBs) are potent vasodilators and often used as a first or second line drug in management of hypertension. Amlodipine, is a longer acting DHP, no longer considered as L-type-specific Ca^{2+} channel blockers (Figure 1). Studies have shown, that amlodipine and cilnidipine blocked N-type Ca^{2+} channels as well.[10-12] Amlodipine along with benidipine, cilnidipine, nicardipine, and barnidipine significantly blocked N-type and P/Q-type Ca^{2+}channels . Amlodipine profoundly blocks the N-type Ca(2+) channels with high affinity[(3)H]amlodipine (K(d), 3.08nM and high potency (IC(50), 2.7 microM at -60mV.[13]

Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle cells and myocardial cells. It is a peripheral arterial vasodilator that acts directly on vascular smooth muscles

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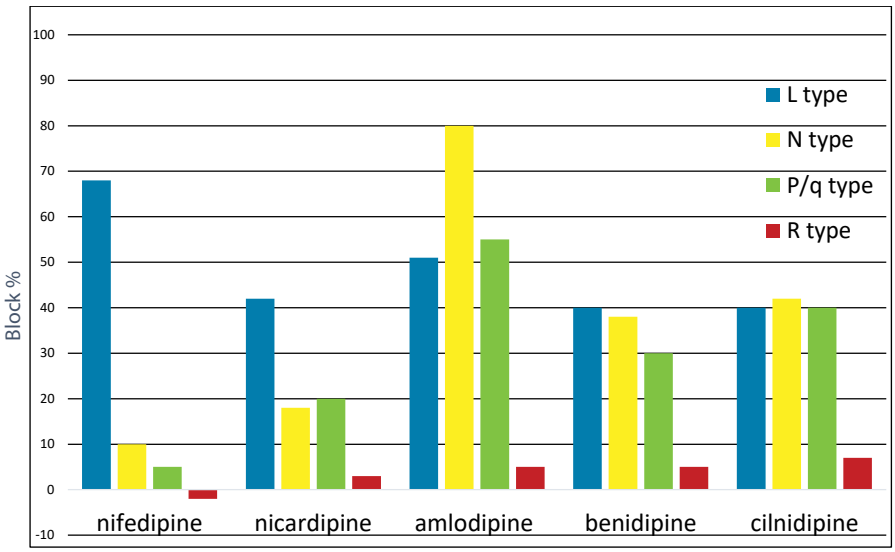

Adapted from Furukawa T et al. J Pharmacol Exp Ther 291 (2), 464-473. 11 1999[13]

Fig. 1: Comparison of the potencies of various DHPs in blocking four subtypes of Ca2+ channels: L-, N-, P/Q-, and R-types

to reduce the peripheral resistance and reduction of blood pressure. The process of contraction is dependent on the movement of extracellular ca^{2+} ions into these cells through specific ion Channel. Amlodipine has a half-life of 35-40 h, longest among all CCBs. It is usually dosed on a once daily basis which is favourable for patient compliance. [14]

A starting dose of 5 mg is usually recommended with a maximum daily dose of 10 mg. In the elderly population and those with hepatic failure, a starting dose of 2.5 mg is recommended. Amlodipine has a gradual onset of action and hence no significant reflex neuroendocrine activation. Activating reflex mechanisms, such as increased peripheral vascular resistance and elevated heart rate, can cause negative effects on lipid and carbohydrate metabolism.[14] These notable adverse effects are commonly seen with other agents including the first generation β-blockers (BBs; such as atenolol and metoprolol) and earlier generation of DHPs. Amlodipine has a high bioavailability, ranging from 60% to 80%; it undergoes hepatic metabolism and shows some impaired elimination in the setting of liver cirrhosis but no accumulation with renal failure. Amlodipine also has a slow rate of elimination over 40–60h. If amlodipine is discontinued, BP generally returns to baseline over 1 week without any dangerous rebound elevations in BP (unlike clonidine).[15] Novel type of CCBs have been developed which have additional properties of blocking T and N subtypes of calcium channels and apart from their class effects they exerts specific action on heart rate and renin aldosterone system. Cilnidipine through its dual L/N-type calcium channel blocker property presumed to effectively suppress neurohumoral regulation of cardiovascular system by inhibition of sympathetic over-activity and modulation of the renin-angiotensin-aldosterone system. In addition to blood pressure lowering effects these novel drugs are anticipated to provide organ protection in management of hypertension.[16]

24 Hours BP Control

Both the magnitude of BP reductions and the control of BP variability may be important in the prevention of Cardiovascular and cerebrovascular events. Ambulatory blood pressure monitoring (ABPM) provides an opportunity to obtain measurements of BP throughout the 24 h period during an individual's normal daily routine. Amlodipine has the longest elimination half-life and slow receptor dissociation kinetic, it shows a gradual and prolonged reduction in BP. A high trough to peak concentration (T:P =0.85) and high smoothness index (SI) indicates that amlodipine is consistent in BP reduction throughout 24 hours.[17] In a meta-analysis of 5188 patients in 11RCTs, amlodipine 5mg and telmisartan 80mg had similar SI which was higher than all ARBs.[18] Across the CCBs, the 24h SI value for amlodipine 5mg was higher than those of manidipine, lercanidipine, nifedipine felodipine and diltiazem.[17]

Blood Pressure Variability

BP variability (BPV) is independent risk factor for CVD events and target organ damage.[17, 19] A 3 year follow up study by Sander et al[20] has shown that greater than 15-mm Hg s.d. of daytime SBP increases the risk of development of early atherosclerosis and CV events. Early morning BP surges (EMBPS) a transient increase in both Systolic BP (SBP) and diastolic BP (DBP) during the morning hours around the time of rising, is one pattern of variability linked with target organ damage and cerebrovascular events. A 10-mm Hg increase in the EMBPS has been shown to increase stroke risk by 22%, independent of age and average 24 h BP.[21] Also a long-term increase in average BP values is risk factor for endothelial dysfunction leading to atherosclerosis, and a relatively short term exaggerated BPV may trigger an atherothrombotic CVD event.[17]

According to Anglo Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm (ASCOT-BPLA) trial a good control of mean BP but greater residual SBPV had a 5 times higher risk of stroke than those with lower variability values hence Visit-visit variability (VVV) is a key predictor of the long-term risk of stroke after transient ischemia. ASCOTBPLA compared Amlodipine-based regimens with Atenolol-based regimens in 19,257 patients with hypertension and other vascular risk factors. It was found that within-visit, VVV and ABPM BPV were all reduced by amlodipine irrespective of its effect on mean BP, whereas BPV increased with Atenolol-based regimen. A significant reduction in CV event, mortality and stroke was observed in amlodipine group compared to atenolol.[22] Similarly in the XCELLENT trial Amlodipine significantly decreased daytime, night-time and 24-hrs SBPV; whereas Indapamide SR significantly decreased SBPV in the daytime and 24 hours. Amlodipine was efficacious across all time-frames even after adjustment for mean BP reduction.[23] Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that even after

adjusting for mean BP, Amlodipine and Chlorthalidone reduced VVV BPV to a greater extent than Lisinopril.[24] A pooled analysis of five studies (47,558 BPV-evaluable patients, duration varied from 4 months to 6 years) showed that BPV with amlodipine was significantly ($P < .0001$) lower compared to atenolol, lisinopril, enalapril. Treatment difference (standard error) was −1.23 (0.46; $P = .008$) mm Hg for amlodipine vs all active comparators.[25] these findings suggest that amlodipine is effective for minimizing BPV.

Side Effect Profile

The most commonly reported adverse effect hindering compliance with amlodipine is peripheral oedema. However, this adverse effect can be minimised if the agent is given at bedtime, and lower doses (2.5 or 5 mg/day) are used. Other reported side effects include dizziness, fatigue, headache, palpitations and nausea, although these are generally not bothersome enough to cause discontinuation of the drug. Also, its vasodilatory effect can lead to decreased cardiac output in the setting of aortic stenosis.[14]

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) cause post capillary dilation and normalize hydrostatic pressure, and are thus ideally suited for prevention/reversal of CCB-induced oedema. ARB/CCB and ACEI/CCB combination therapy is also more effective than CCB monotherapy in controlling blood pressure. These combinations represent an important advance in the management of hypertension. Although the incidence of oedema recorded in the CCB monotherapy groups varies widely (range, 4.9–34.4%), the data are consistent in showing lower rates of this side effect in the patients who receive ACEI/CCB or ARB/CCB combination therapy.[26] For example addition of olmesartan medoxomil 40 mg to amlodipine 10 mg reduced the placebo-subtracted rate of oedema by more than 50%.[27] In an additional study, the incidence rate of peripheral oedema was lower with valsartan and amlodipine in combination (5.4%) than with amlodipine monotherapy (8.7%).[28]

Amlodipine in Diabetes with Microalbuminuria

Endothelial dysfunction alters the structural and functional effects on the target vessel. Endothelial dysfunction within the glomerular basement membrane may modify glomerular barrier permeability, thus leading to the excretion of albumin into the urine.[29] In diabetic patients presence of microalbuminuria helps in early diagnosis of incipient diabetic nephropathy. Microalbuminuria is considered as an independent risk factor for renal impairment, cardiovascular disease and premature mortality.[30] An early intervention may retard the progression to end-stage renal disease (ESRD). CCBs are not always able to protect against kidney injury, as was shown in the Renoprotection in Patients with Nondiabetic Chronic Renal Disease (REIN)-2.[31] And, in Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension (GUARD) trials, the antialbuminuric effect of CCB was weaker than that of diuretics in RAS inhibitor-treated hypertensive patients with type 2 diabetic nephropathy.[32] The uncertain renoprotective effects of L-type CCBs may be due to the presence of L-type calcium channels at the afferent but not efferent arterioles. L-type CCBs cause afferent arteriole-specific vasodilation, which increases the glomerular pressure. This adverse action of L-type CCBs in the glomerular microcirculation counteracts their ability to attenuate glomerular hypertension through the systemic decrease in BP. Thus, the use of L-type CCBs is not always beneficial in patients with renal dysfunction. In contrast, L/ N -type CCBs are able to inhibit renal sympathetic nerve activity and cause efferent arteriolar vasodilation. Thus, protect the glomeruli through the attenuation of glomerular hypertension. Since, L-type calcium channels do not express in glomerular efferent arterioles, the renoprotective effects of an L-type CCB are expected to be lower than those of an L-/N-type CCB. [33]

However in SAKURA trial,[34] L-/N-type CCB cilnidipine did not result in a greater antialbuminuric effect than L-type CCB amlodipine in RAS inhibitor-treated hypertensive patients with diabetes and microalbuminuria. The UACR was seemingly decreased after 3 or 6 months of treatment; In cilnidipine group, UACR seems to be decreased largely to 85.05 mg/g (-23.72% reduction compared to baseline) in 3 months, 81.71 mg/g (-26.72% reduction) in 6 months, whereas in amlodipine group, UACR decreased to 75.73 mg/g (-14.23% reduction) in 3 months, 78.53 mg/g (-11.05% reduction) in 6 months. However, UACR tended to return to the baseline value after 12 months of treatment with either drug. The change in the natural logarithm of the UACR after 12 months of treatment was -0.21 ± 0.69 in the cilnidipine group and -0.21 ± 0.86 in the amlodipine group. The difference between the groups was estimated to be 0.00 (95% confidence interval: -0.16 to 0.17, $P = 0.96$). Thus, cilnidipine and amlodipine had similar effects on UACR in hypertensive patients with diabetic microalbuminuria. CKD stage was unchanged in 96 vs 89 patients, advanced in 20 vs 21 patients, and regressed in 26 vs 34 patients after treatment with cilnidipine and amlodipine respectively.

In diabetes, the main mechanisms of glomerular hyperfiltration (which may underlie the initiation and progression of DN) are by increases in the levels of hormones, such as insulin-like growth factor 1, atrial natriuretic peptide, intracellular accumulation of sorbitol and protein glycosylation, and activated tubuloglomerular feedback, which are caused by increased tubular sodium reabsorption through hyperinsulinemia and hyperglycemia. Sympathetic nerve activation is not thought to be a major mechanism of glomerular hyper filtration in DN.[51,52] The lack of a clear difference in the antialbuminuric effects of cilnidipine and amlodipine in the present study may be due to the marginal contribution of sympathetic nerve activation to the progression of DN.[35]

Amlodipine and Atherosclerosis

Amlodipine has a potential benefit in atherosclerosis. It prevents the formation of free radicles thus averting the oxidative damage to the lipid bilayer.[14] Zhang and Hintze in preclinical study found that amlodipine increased NO production in canine coronary microvasculature, which could be another plausible anti atherosclerotic effect.[36] Additionally,

Table 1: Cardiovascular event and outcome with amlodipine in landmark trials

	Trials	Intervention	No.of patients	No. events odds ratio 95%(CI)					
				Stroke	MI	CHF	MACE	Total mortality	CV mortality
AML vs ACEi	AASK[43]	Ramipril	436	23	19	20	89	34	12
		Amlodipine	217	9	5	8	28	23	7
				OR 0.78 (0.35-1.71)	OR 0.52 (0.19-1.41)	OR 0.80 (0.34-1.84)	OR 0.58 (0.36-0.92)	OR 1.33 (0.76-2.34)	OR 1.18 (0.46-3.04)
	ALLHAT[44]	Lisinopril	9054	457	796	612	2514	1314	618
		Amlodipine	9048	377	798	706	2432	1256	603
				OR 0.82 (0.71-0.94)	OR 0.99 (0.90-1.08)	OR 1.17 (1.04-1.31	OR 0.96 (0.90-1.02)	OR 0.95 (0.87-1.03)	OR 0.97 (0.87-1.09)
AML vs ARBs	VALUE[45] 2004	Amlodipine	7596	281	313	400	1298	818	304
		Valsartan	7649	322	369	354	1349	840	304
				OR 0.87 (0.74-1.03)	OR 0.85 (0.73-0.99)	OR 1.15 (0.99-1.33)	OR 0.96 (0.89-1.05)	OR 0.98 (0.88-1.08)	OR 1.01 (0.86-1.18)
	IDNT[46] 2003	Amlodipine	567	15	27	93	161	83	37
		Irbesartan	579	28	44	60	172	87	52
				OR 0.53 (0.28-1.01)	OR 0.61 (0.37-1.00)	OR 1.70 (1.20-2.40)	OR 0.94 (0.73-1.21)	OR 0.97(0.70-1.34)	OR 0.71 (0.46-1.10)
	CASE J[47] 2008	Amlodipine	2349	47	18	16	134	86	15
		Candesartan	2354	60	17	20	134	73	11
				OR 0.78 (0.53-1.15)	OR 1.06 (0.55-2.06)	OR 0.80 (0.41-1.55)	OR 1.00 (0.78-1.28)	OR 1.19 (0.86-1.63)	OR 1.37 (0.63-2.99)
AML vs Diuretic	ALLHAT[44] 2002	Chlorthalidone	15255	675	1362	870	3941	2203	996
		Amlodipine	9048	377	798	706	2432	1256	603
				OR 0.94 (0.83-1.07)	OR 1.00 (0.91-1.11)	OR 1.40 (1.26-1.55)	OR 1.06 (0.99-1.12)	OR 0.95 (0.89-1.03)	OR 1.02 (0.92-1.14)
	ACCOM-PLISH[48] 2008	Amlodipine	5744	112	125	100	552	236	107
		HCTZ	5762	133	159	96	679	262	134
				OR 0.84 (0.65-1.09)	OR 0.78 (0.62-0.99)	OR 1.05 (0.79-1.39)	OR 0.80 (0.71-0.90)	OR 0.90 (0.75-1.08)	OR 0.80 (0.62-1.03)
AML vs BB	ASCOT-BLPA[41]	Amlodipine	9639	327	429	134	1193	738	263
		Atenolol	9618	422	474	159	1438	820	342
				OR 0.77 (0.66-0.89)	OR 0.90 (0.79-1.03)	OR 0.84 (0.67-1.06)	OR 0.80(0.74-0.87)	OR 0.89 (0.80-0.99)	OR 0.76 (0.65-0.90

Adapted from Seung-Ah Lee et al. Korean J Intern Med 2014;29:315-324[42]; AASK The African American Study of Kidney Disease and Hypertension; ALLHAT Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; IDNT Irbesartan diabetic nephropathy trial; ASCOT Anglo-Scandinavian Cardiac Outcomes Trial; VALUE Valsartan Antihypertensive Long-Term Use Evaluation; CASE J Candesartan Antihypertensive Survival Evaluation in Japan ; ACCOMPLISH The Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension trial; AML amlodipine, RAM Ramipril, MET Metoprolol, CT chlorthalidone, LIS lisinopril, ATN atenolol, VAL valsartan; HCTZ hydrochlorthiazide

amlodipine has been shown to up regulate the expression of interleukins, which may also have antiproliferative effects, and to have favourable effects on extracellular matrix remodelling.[37]

The PREVENT trail was a placebo controlled prospective randomized trial to study the effect of amlodipine upon atherosclerotic progression in patient with established CAD. Amlodipine reduced the progression of atherosclerosis in the carotid arteries as assessed with B-mode ultrasonography. Amlodipine had a significant effect in slowing the 36-month progression of carotid artery atherosclerosis: the placebo group experienced a 0.033-mm increase in Intima Media Thickness. Amlodipine also reduced coronary revascularizations (53 versus 86, HR 0.57 [0.41 to 0.81]) regardless of the use of β-blocker, nitrates, or lipid-lowering therapy. Fewer events in the amlodipine group compared to placebo (86 versus 116, HR 0.69 [0.52 to 0.92]), mostly attributable to a difference in unstable angina and revascularization. These beneficial effects were not seen in previous angiographic trials with nifedipine or nicardipine in patients with stable coronary artery disease even though with proved antianginal effects, suggestive of fact that amlodipine may have an additional effects.[38]

The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine and enalapril, with placebo in normotensive patients with CAD. Amlodipine group vs placebo (P=.12), showed a trend towards less progression of atherosclerosis which was significant in patients with higher systolic blood pressure.[39]

In the randomised trial Coronary Angioplasty Amlodipine Restenosis Study (CAPARES), patients had a reduced incidence of repeat percutaneous transluminal coronary angioplasty when treated with amlodipine.[40]

Amlodipine and Angina

Antianginal efficacy of amlodipine, is mediated by the amlodipine-induced dilation of coronary arteries and reduction in total peripheral resistance, decreasing the occurrence of symptomatic angina, and silent MI.[14] In the PREVENT trial wherein 68 % of participant had history of angina, amlodipine showed a significant reduction in hospitalization for unstable angina compared to placebo (HR: 0.67, 95% CI: 0.48–0.93).[38] In ASCOTBPLA, amlodipine vs atenolol significantly reduced unstable angina (HR: 0.68, 95% CI: 0.51–0.92; *P* <0.0115) but had no significant effect on chronic stable angina (HR: 0.98, 95% CI: 0.81–1.19).[41] 89% patients enrolled In CAMELOT trial had history of Angina, the rate of hospitalization for angina showed a statistically significant difference between amlodipine and enalapril (HR, 0.59; 95% CI, 0.42-0.84, P=.003) and amlodipine vs placebo (HR 0.58; 95% CI,0.41-0.82,P=.002 This study suggests that normotensive patients treated with amlodipine show reduced rates of CV events and hospitalisations for angina compared with enalapril.[39]

Table 2: Comparative analysis of amlodipine and cilnidipine

	Amlodipine	Cilnidipine	Comments
24 h BP control	long half-life of 35-50h,	Shorter half-life 2.5h	Amlodipine shows a good BP control for 24h
Blood pressure variability (BPV)	Reduces BPV	Not known	Amlodipine minimises BPV reducing the risk of cv and cerebrovascular events
Ca channel blockade	Blocks L and N ca channels.	Blocks L, N ca channels	Both are Non selective DHP
Pedal edema	Dose dependent and reversible.	Relatively less	Benefits outweighs pedal edema with the use of amlodipine.
CV outcome trials	Reduction in primary and secondary points (composite of fatal non fatal MI, HF, angina, stroke, CV mortality, total mortality)	Human data is unavailable	Amlodipine offers proven CV mortality and CV events reduction in large multicentric trials.
Stroke reduction	Proven stroke reduction through long terms outcome trials	No proven benefits in stroke reduction	Amlodipine offers stroke reduction
Renal outcomes (ESRD)	Reduces the progression of CKD.	No large trials available	Amlodipine has proven reduction in progression to ESRD in large multicentric trials.
Antiproteinuric effect	Similar antiproteinuric observed in diabetic patients with proteinuria(SAKURA TRIAL)[34]	Similar antiproteinuric observed in diabetic patients with proteinuria	Both have role in Renoprotection
Affordability	Less costly	More costly	Amlodipine is a cost effective therapy

Amlodipine and Cardiovascular Outcomes

Amlodipine has been most widely and extensively studied CCB. Its effect on cardiovascular outcomes in hypertensive patient are evaluated in many outcome trials.[42] A data of around 87000 patients who were enrolled in different trials for a duration of 3-6years has been shared in Table 1.

A significant reduction in cardiovascular events and total mortality was observed with amlodipine compared to other antihypertensive agents. Risk of MI was significantly decreased with amlodipine compared to other antihypertensives. Also amlodipine showed better results in stroke prevention. CHF incidence seemed to be increased with amlodipine compared with ACE inhibitors or ARBs, but was comparable to that with ß-blockers and diuretics Amlodipine can be safely used in high-risk cardiac patients and is associated with benefits for all major cardiovascular endpoints as well as total mortality.[41,42,48] Newer CCBs like Cilnidipine have been introduced shortly and clinical data on long term cardiovascular outcomes trials are still lacking. Few animal studies are available in support of cardio protective benefits of Cilnidipine. In a preclinical study for MI, Cilnidipine showed a decrease in the myocardial interstitial norepinephrine levels during ischemia and reperfusion periods, leading to reduction of the myocardial infarct size and occurrence of ventricular premature beats.[49] Likewise, in vivo experimental data have stated that cilnidipine shows antianginal effects in the experimental model of vasopressin-induced angina and improvement of the ventricular repolarization in the canine model of long QT syndrome.[50,51] Large multicentric trials in support of the above findings are still the need of hour. Whereas amlodipine is backed with sufficient evidences to support the above findings.

Amlodipine and Renal Outcomes

Hypertension is a major cause of end stage renal disease (ESRD), and blood pressure levels have been shown to be correlated with renal disease progression. A strict BP control is the mainstay of treatment to prevent renal progression and to reduce cardiovascular risk in hypertensive patients with chronic kidney disease (CKD).[52] ALLHAT found no significant differences between amlodipine vs diuretic in the development of ESRD or renal disease progression (by estimated glomerular filtration rate [(GFR]) in high risk hypertensive patients.[44] CASE-J also noted no significant difference in rates of renal events between candesartan- and amlodipine-treated high-risk hypertensive patients (HR: 0.70, 95% CI: 0.39–1.26; P <0.23).[47] Considerable clinical evidences suggest that an inhibitor of the renin–angiotensin system (RAS), such as an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin II type 1 receptor blocker (ARB), has an apparent renoprotective effect. Adequate BP levels are seldom achieved with only one RAS inhibitor. A combination of two to three antihypertensive drugs is required to decrease BP to target levels, especially in patients with kidney disease.[52] ACCOMPLISH found that using the progression of chronic kidney disease endpoint comprised of doubling of serum creatinine, ESRD, and dialysis, treatment with an ACE-inhibitor (benazepril) plus amlodipine was associated with significantly reduced risk of kidney disease progression compared to treatment with ACE inhibitor plus a diuretic (hydrochlorothiazide) (HR: 0.52, 95% CI: 0.41–0.65; P, 0.0001). In elderly patients >65 years age amlodipine group showed 70% RRR in progressing to dialysis compared to HCTZ group (p=0.053, for the difference). In the intention-to-treat population, the amlodipine group had a 48% RRR for chronic kidney disease (CKD) progression, defined as doubling of serum creatinine, estimated glomerular filtration rate (eGFR) <15 mL/min, or dialysis compared with the HCTZ group.[48]

Conclusion

Amlodipine is a superior option in the HTN armamentarium, not only for controlling BP but also for safely improving patient outcomes (Table 2). There has been a vast clinical experience with its use both as monotherapy or combination in varied condition. It has proven benefits in angina with lesser hospitalization and fewer revascularization rates. Its unique mechanism and property has shown benefits in reduction of progression of atherosclerosis. Amlodipine unlike newer CCBs, has shown robust reduction in cardiovascular endpoints particularly stroke. Even in renal impaired patients, amlodipine with effective BP control over 24hrs reduces the progression of ESRD. Hence, compared to all the CCBs, amlodipine still stands the test of time.

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