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# Medical Bulletin

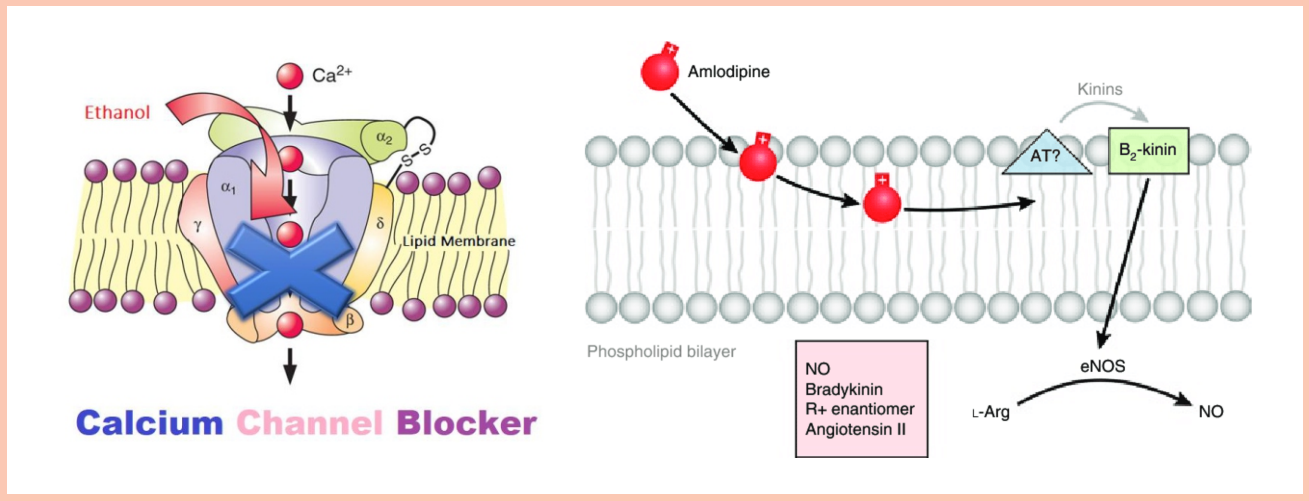
EXCEL Division of Blue Cross Laboratories Pvt Ltd.

## CURRENT MANAGEMENT OF HYPERTENSION: AMLODIPINE

Hypertension is the leading cause of death worldwide, affecting 1.4 billion people. Hypertension becomes progressively more common with advancing age, with a prevalence of more than 60% in people aged 60 years or older. Observational studies and clinical trials reported that short and long term blood pressure variability (BPV) are linked to hypertension mediated target organ damage, cardiovascular events, and mortality.

Calcium channel blockers (CCBs) were first introduced for coronary heart disease but gained widespread recognition for their efficacy in hypertension. These agents can be classified into dihydropyridines, phenylalkylamines, and benzothiazepines. Although all CCBs share the same ability to interact with L-type voltage-dependent transmembrane calcium channels, they have distinctive pharmacokinetics and pharmacodynamics that influence their efficacy and safety profile.

Amlodipine has unique characteristics that set it apart from other drugs within this class. Compared to other dihydropyridine agents, amlodipine has low renal clearance (7 mL/min/mg) and long half-life (35−50 h). Amlodipine has a high bioavailability (60%−80%) and sustains its antihypertensive effect for more than 24 h following a single oral dose, which is beneficial for patient compliance. In addition, BP control is maintained even when a dose has been missed, which is the most common form of noncompliance in the management of hypertension. Side effects of amlodipine include edema, palpitations, dizziness, and flushing, which are more common with the higher dose of 10 mg.




*Amlodipine, not only penetrate the plasma membrane to interact with the L-type calcium channel, but also have additional biologic or pleiotropic actions independent of their interaction with the calcium channel.*

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## ROLE OF AMLODIPINE IN MILD TO MODERATE HYPERTENSION; BPV & MORNING BP SURGE

Amlodipine is effective in reducing mean BP in patients aged ≥50 years. In Asians with mild to moderate hypertension, amlodipine titration from 5 to 10 mg/day significantly reduced systolic blood pressure (SBP).

BPV over 24 h is a significant and independent risk factor for cardiovascular morbidity and mortality. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) treated with Amlodipine had a significantly lower BPV. CCBs reduced inter-individual BPV more than all other classes of drugs.

The morning BP surge is linearly associated with risk of stroke and can be reduced when antihypertensive drugs are taken in the evening compared with in the morning. This reflects the fact that many drugs are not completely effective over a 24-h dosing interval. Thus, long-acting drugs are more likely to be effective in reducing the morning BP surge. Within the dihydropyridine class of CCBs amlodipine is associated with significantly greater reductions in morning BP surge.

## ROLE OF AMLODIPINE IN STROKE PREVENTION

Many landmark trials have shown the benefit of amlodipine protection against stroke. Several mechanisms have been proposed to explain the benefits of amlodipine as: (1) Amlodipine has a longer duration of action than almost all other antihypertensive drugs; (2) Carotid intima-media thickness (IMT) is strongly correlated with cardiovascular events. Amlodipine, can reduce the progression of carotid IMT more than diuretics, β-blockers, or angiotensin converting enzyme inhibitors (ACE-I), and this might contribute to its superior protection against stroke.

## AMLODIPINE IN PATIENTS WITH ANGINA PECTORIS

About 47% of the risk of developing ischemic heart disease is attributable to hypertension. Both the European Society of Cardiology (ESC) and the American Heart Association (AHA) recommend CCBs alone, or in combination with a β-blocker, as first-line treatment in the management of stable ischemic heart disease. In patients with hypertension and type 2 diabetes, amlodipine therapy resulted in a significantly greater reduction of IMT compared with ARB therapy, suggesting amlodipine has an inhibitory effect on early atherosclerotic process.

### PATIENTS WITH DIABETES MELLITUS / CHRONIC KIDNEY DISEASE

The 2023 American Diabetic Association (ADA) guideline recommends CCBs as first-line therapy for patients with diabetes without albuminuria and coronary artery disease, as in the absence of albuminuria, ACE-Is and ARBs do not seem to offer superior cardiovascular protection. A database analysis showed that morning BPV was lower in patients with type 2 diabetes treated with CCBs than that in those treated with ARBs and/or ACE-Is.

The long-term follow-up of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that patients with kidney dysfunction treated with amlodipine retained higher mean levels of eGFR. In a real-world-evidence study, while showing kidney protection similar to other CCBs, amlodipine showed higher potency by triggering greater BP reduction at lower doses. Amlodipine is also recommended for lowering BP in patients on hemodialysis.

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## OLDER PERSONS WITH HYPERTENSION

In persons 65 years or older, diuretics and CCBs are preferred for patients with isolated systolic hypertension and marked BPV. CCBs have an advantage over diuretics because they do not affect electrolytes. Results from Systolic Blood Pressure Intervention Trial (SPRINT) had a lower rate of cardiovascular events (MI, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes).

To conclude, amlodipine is effective in managing hypertension in patients with SBP/DBP of 140/90 mm Hg or higher, including those at low risk of cardiovascular disease and those with established cardiovascular diseases. Mean BP and BPV control are crucial in reducing the risk of cardiovascular events. Amlodipine not only provides 24-h BP control but also effectively reduces BPV, thereby protecting against stroke and MI. Furthermore, amlodipine effectively controls BP in different ethnic groups, older adults, patients with diabetes, and patients with chronic kidney disease without worsening glycemic and kidney function.

***Source:*** *Ji-GuangWang, et.al; Clin Hypertens. 2023;25:801–807. Mason R P et.al;Arterioscler Thromb Vasc Biol.2003.*

# THE ROLE OF FOLATE, VITAMIN B12 & B6 IN HYPERHOMO-CYSTEINEMIA AS THE RISK FACTOR OF CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD), encompassing ailments affecting the heart and vascular system, is estimated to contribute to one-third of global mortality, and its prevalence is continuously rising. The etiology of this condition is multifactorial, making it challenging to identify a singular causative factor. Homocysteine, is known to contribute to the development of atherosclerotic vascular disease and hypercoagulability.

However, the body does not produce them naturally and they need to be obtained from dietary intake. B vitamins are a collection of chemical compounds that play a crucial role in physiological function. Vitamin B6, folate (B9), and vitamin B12, are classified as water soluble vitamins. B vitamins work as coenzymes in the majority of enzymatic reactions that facilitate all aspects of cellular physiological activity.

The vitamin's biologically active form acts as a coenzyme by binding to the protein "apoenzyme" to generate a “holoenzyme". This process enhances the enzyme's ability to catalyze a wider range of processes. In general, the actions of B vitamins can be split into their roles in catabolic metabolism, which generates energy, and anabolic metabolism, which involves the creation and alteration of bioactive molecules.

Vitamins B6, B9, and B12 are crucial in the metabolism of homocysteine. Homocysteine (Hcy) is a non-dietary amino acid that can be transformed into cysteine or regenerated into methionine, an essential amino acid, with the assistance of specific B vitamins.

The concentration of homocysteine is controlled by two primary pathways: remethylation, which converts it back to methionine, or transsulfuration, which converts it to cysteine while also producing hydrogen sulfide (HS). Elevated homocysteine levels, condition characterized by the presence of more than 15 micromol/L of homocysteine in the blood, can be attributed to a range of variables, such as genetic predisposition, dietary choices, lifestyle habits, and certain drugs. One of the common cause of hyperhomocysteinemia is believed

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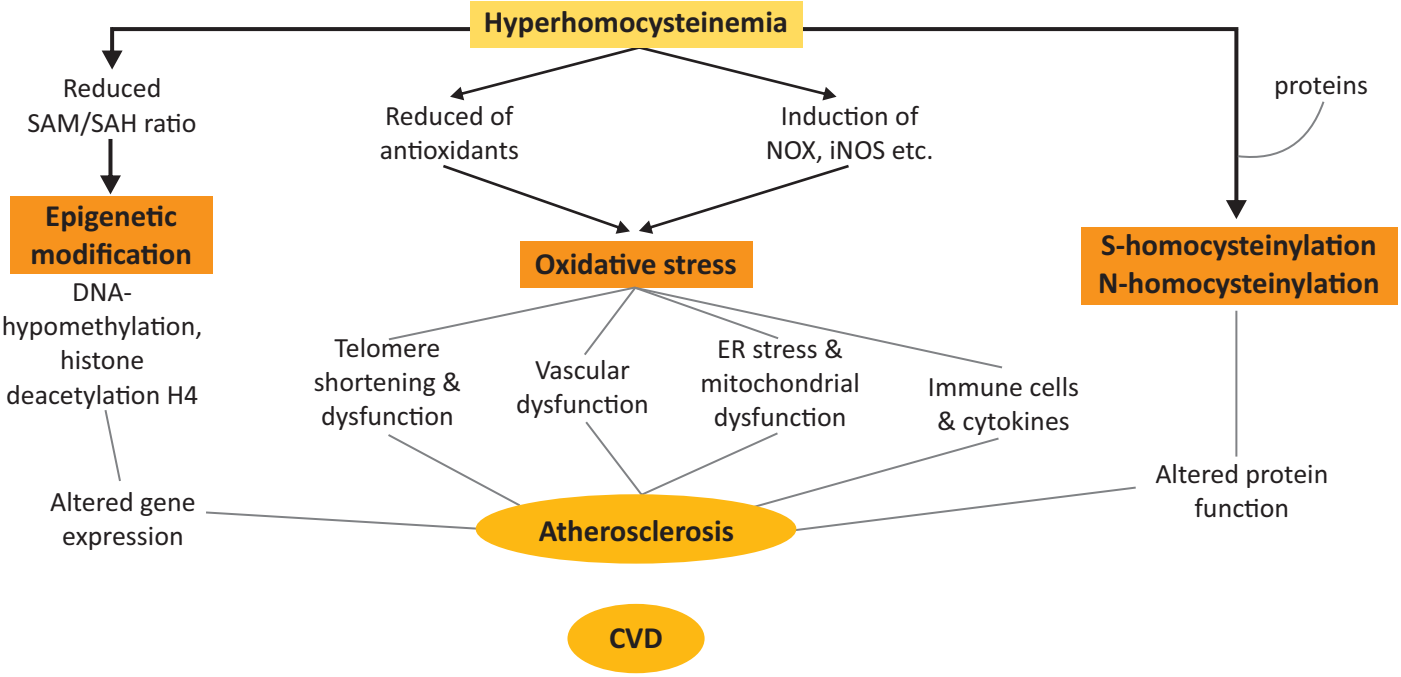


*Pathomechanism of hyperhomocysteinemia. The role of oxidative stress, epigenetic modifications, changes in protein function, causing atherosclerosis and cardiovascular disease. SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; NOX, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; iNOS, inducible nitric oxide synthase; ER, endoplasmatic reticulum.*

to be a deficiency of certain vitamins, particularly folate, B12, and B6,which are important for effectively recycling homocysteine in the methionine cycle. Vitamin B is intricately linked to both the homocysteine and cardiovascular disease (CVD) pathways.

Hyperhomocysteinemia has the potential to induce damage to endothelial cells via multiple intracellular mechanisms & has been linked to an elevated risk of cardiovascular disease as seen in Figure above, cerebrovascular disease, and thromboembolism. Thus, lowering homocysteine levels has been proven to decrease these cardiovascular risks and various studies support the supplementation with vitamins (B6,B9,B12) have decreased the homocysteine levels.

The 2023 guidelines published by the American Heart Association (AHA)/American Stroke Association (ASA) incorporated the use of homocysteine-lowering therapy with folic acid, and B12 in the form of methylcobalamin, for both primary and secondary prevention of ischemic stroke.

***Source:*** *Muhammad Yatsrib Semmeet.al; Healthy Tadulako Journal / Vol 10 No.3 Juli 2024.*

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