Review Article

Role and complication of existing and newer calcium channel blockers in hypertension treatment

Abstract

Hypertension is the major culprit for cardiovascular disease and early death worldwide. Early and prompt management of hypertension can significantly prevent complications. Owing to the extensive usage of antihypertensive drugs, worldwide mean blood pressure has stayed constant or declined to some extent during the previous four decades although high prevalence in reported in developing countries. CCBs are a class of drugs that are commonly used to lower blood pressure and are structurally and functionally diverse. They are generally well accepted and have less adverse effects. The purpose of this research is to review the available information about role and complication of existing and newer CCBs in hypertension treatment. As soon as CCBs were utilized to treat hypertension, they earned a reputation as potent antihypertensives that significantly and consistently lowered blood pressure in people of all ages and races in mono and combination therapy. CCBs work by reducing peripheral vascular resistance. Newly available CCBs may be therapeutically more effective in treatment of hypertensive individuals with chronic kidney disease than the L-type CCB. Lercanidipine is a third generation CCB that has fewer side effects and is used in people with a high risk of target organ damage and elderly patients. CCBs are associated with certain side effects including peripheral edema, hypotension, headaches, conduction abnormalities among various others. Some studies have also associated use of CCBs with modest risk increase for myocardial infarction and heart failure. Further clinical research is required to elaborately study the efficacy of CCBs in management of hypertension.

Keywords: *hypertension, side effects, blood pressure, CCB*

Introduction:

The principal cause of disability-adjusted life years globally is hypertension, which is also the main risk factor for cardiovascular disease. The most frequent risk factor for cardiovascular disease and cerebrovascular disease, including ischemic heart disease (55%), peripheral arterial disease (58%), heart failure (58%) and haemorrhagic stroke (50%) is suboptimal

blood pressure (BP) regulation. In addition, hypertension is a major contributor to dementia brought on by cerebral small vessel disease, chronic kidney disease, the progression of kidney disease, and end-stage kidney disease. Worldwide, hypertension is widespread and is getting worse with a prevalence of 31%, or over 1.4 billion individuals. Hypertension is defined at the systolic BP/ diastolic BP criterion of greater than 140/90 mm Hg. A fatal cardiovascular event's risk doubles for every 20-mm Hg increase in systolic BP or 10-mm Hg increase in diastolic BP (1). Current international guidelines advocate reducing BP in all individuals with hypertension until systolic and diastolic readings of less than 140/90 mm Hg are achieved. Regardless of gender, age, ethnicity, or any additional concurrent clinical conditions, these BP objectives are advised for all adult patients with hypertension (2, 3).

Calcium channel blockers (CCBs) are drugs that effectively reduce BP by dilating blood vessels via limiting calcium flow into cells. Irrespective of gender, race or ethnicity, age, or dietary sodium intake, CCBs lowers BP in all patient populations (4). CCBs prevent the movement of extracellular calcium through cell wall-spanning ion-specific channels. Although there are various kinds of these channels, the L-type channels are inhibited by the CCBs that are now present in the market. Vascular smooth muscle cells relax when inward calcium flux is blocked, which causes vasodilation and a decrease in BP. Contractility is decreased, and sinus pacemaker and atrioventricular conduction velocities are retarded in the heart muscle (5). There are two normally employed CCB classes, each having unique effects on myocardial inotropism and vasodilation. One is dihydropyridines, which decrease BP by dilating the arteries. These include clevidipine, amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, and nisoldipine. Another is non-dihydropyridines, which act by lowering heart rate and contractility while modestly enhancing artery dilation, such as diltiazem and verapamil (6).

Patients with truly resistant hypertension have also shown that CCB-based therapy is quite successful and secure, especially when paired with renin angiotensin system (RAS)-blocking medications either Angiotensin converting enzyme (ACE) inhibitors or Angiotensin receptor blocker (ARB), thiazide diuretics, and anti-aldosterone medications. In these situations, high dose, integrated, and synergistic antihypertensive treatments are necessary to attain the targeted BP measurements, even with high medication adherence and minimal risk of adverse drug reactions. So, in this clinical situation of high-risk patients with real resistant hypertension, CCBs constitute a highly attractive and helpful partner for any antihypertensive therapy (7-9). The majority of negative effects of CCBs are predictable based on their

pharmacological activity and may be simply categorized into the various types including vasodilatation, adverse inotropic effects, conduction disruptions, gastrointestinal effects, metabolic effects, and medication interactions are only a few of the potential side effects. Nifedipine increases the likelihood of vasodilatory symptoms such palpitations, flushing, headaches, and dizziness. Nifedipine also frequently causes peripheral edema, while the exact cause is unknown. Verapamil, followed by diltiazem, and nifedipine, have the most adverse inotropic effect for a given level of vasodilation. In hypertensive individuals with second- and third-degree heart blocks, sick sinus syndrome, and severe heart failure, CCB medications are contraindicated. While nifedipine does not affect cardiac conduction when taken in therapeutic dosages, verapamil and diltiazem do. Verapamil frequently causes local gastrointestinal symptoms including nausea and constipation (10). The purpose of this research is to review the available information role and complication of existing and newer calcium channel blockers in hypertension treatment.

Methodology:

This study is based on a comprehensive literature search conducted on September 21, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about role and complication of existing and newer calcium channel blockers in hypertension treatment**.** There were no restrictions on date, language, participant age, or type of publication.

Results and Discussion:

One of the most important strategies for lessening the burden of hypertension-related cardiovascular and renal illnesses is the effective management of high BP. Despite these tried-and-true ideas, hypertension is still not well-controlled on a global scale. The preferred use of more potent, long-lasting, and well-tolerated antihypertensive drugs, which aims to ensure adherence to prescribed medications, and the extensive use of logical, integrated, and synergistic combination therapies, even as first-line strategies, aims to achieve the recommended BP targets, are two interventions that have been suggested to improve BP control in patients with hypertension. Drugs inhibiting the RAS and CCBs have shown to be effective and safe in lowering BP and achieving the recommended targets with a good

tolerability profile among the potential antihypertensive drug classes presently available for the clinical management of hypertension, both in monotherapy and in combination therapy. In particular, CCBs have become one of the most popular classes of antihypertensive drugs in the past 20 years due to their effectiveness in lowering blood pressure, good tolerability, and evidence showing that they can lessen the effects of hypertension on the cardiovascular system and the kidneys (11).

Role of CCB in hypertension; evidence from literature

The first vasodilator drugs to be widely accepted for the treatment of pulmonary arterial hypertension were CCBs. They have been demonstrated to be especially beneficial in patients who exhibit a significant initial hemodynamic response to pulmonary vasodilators. Currently only these patients are treated with CCB. Only 5% of pulmonary artery hypertension patients are anticipated to benefit long-term from CCB, as per current estimates. Most non-idiopathic forms of pulmonary arterial hypertension are thought to have an even lower response rate. Both the responders and non-responders; who do not respond to CCB should be managed with newer drugs, which are a part of advanced pulmonary arterial hypertension therapy (12). Puscas.et.al stated that the CCBs studied gradually lower arterial BP in hypertensive individuals while gradually bringing erythrocyte carbonic anhydrase I activity in normotensive participants into the normal range. Further sharing their perspective, they described that verapamil and amlodipine have a dual mechanism of action, with their effect on calcium channels constituting the first and most well-known activity. The second mechanism, which the authors proposed, exerts direct action on the carbonic anhydrase I isozyme of the vascular smooth muscle, and its suppression should ensure an appropriate pH for calcium ions to transit through the channels, leading to vasodilation. This dual mechanism, one of which is partially dependent on carbonic anhydrase I inhibition, may account for the hypotensive effects of verapamil and amlodipine (13).

CCBs have been found to be safe for elderly patients and helpful for managing hypertension in all age groups. The most effective of this class of medications is the long-acting or most recent generation of dihydropyridines, which block L-type calcium channels. Numerous studies have shown that these medications are useful for geriatric patients. The most advised method of prescribing long-acting CCBs is as a single dosage. The effectiveness of this pharmacological class in treating hypertension in older patients has been shown to be safe and comparable to other commonly prescribed medications (14). Findings of a meta-analysis

demonstrated that perioperative hypertension was successfully treated with CCB, which was also well tolerated thus for hypertensive individuals who would have surgery, CCBs should be promoted as they have a favourable safety profile and may be useful for controlling postoperative hypertension (15). Results of another meta-analysis concluded that ACE+ARB+CCB therapy is preferable to other antihypertensive treatment regimens because it has a reduced incidence of adverse events and cardiovascular events while having similar effects on decreasing blood pressure and maintaining renal function (16).

Dihydropyridine CCBs are among the first-line antihypertensive medications that are advised in all actual clinical guidelines for the treatment of essential hypertension. Their effectiveness in lowering BP as well as in lowering cardiovascular morbidity and mortality in hypertensive individuals with a normal or high cardiovascular risk profile has been supported by a number of recent large clinical trials. In clinical trials, amlodipine-based therapies were at least as effective as those based on the use of diuretics, beta-blockers, and RAS blockers in decreasing BP and occasionally somewhat more effective in preventing target organ damages (17). Tamargo and Ruilope described in their study that in Far East countries, new dual L-/T- and L-/N-type CCBs including benidipine and efonidipine and CCBs including cilnidipine have been licensed as antihypertensive medications. While L-type CCBs and L/N- and L/T-type CCBs have similar antihypertensive effects, the latter two reduce intraglomerular pressure, enhance renal hemodynamic, and give a higher reduction in proteinuria even in patients on renin-angiotensin-aldosterone inhibitor therapy. However, there are significant biases in clinical trials that purport to show that L/T- and L/N-type CCBs are superior to traditional L-type CCBs in hypertensive patients with chronic renal disease, and their safety profile was underreported (18). Thamcharoen.et.al concluded that L/N- and L/T-type CCBs coupled with a renin-angiotensin-aldosterone system blocker reduced proteinuria and improved kidney function without having any extra effects on BP. Author further suggested that more research is required to determine efficacy of this combination medication (19). The fixed-dose combinations of a calcium channel blocker and an ACE inhibitor have superior tolerability, a lower risk of side effects, more beneficial effects on the target organs, better compliance, and lower costs. For clinical use, a variety of fixed-dose combination strategies to reduce blood pressure are available (20).

The necessity of controlling BP and coexisting diseases is emphasized in new European guidelines, which aim to lower cardiovascular disease risk overall. The cornerstones of antihypertensive therapy among therapeutic choices are CCBs; due to their

adaptability, they can be used in a wide variety of combinations with patients who have particular medical demands. Comparable to other CCBs, lercanidipine is a third generation CCB that has fewer side effects. People with a high risk of target organ damage and elderly patients may want to consider this medication. In order to optimize the clinical benefit and enhance medication compliance, current hypertension management should be customized for each patient (21). The BP-lowering and cardiovascular disease and stroke prevention properties of CCBs are remarkable. Even in heart failure or chronic kidney disease, where CCBs are unlikely to provide optimal results, CCBs may be added when more lowering of BP is required to fulfil rigorous targets. Combining CCBs with anti-neurohumoral medications such as ACE inhibitors is very helpful for maintaining or management of BP, lowering side effects including edema, and improving results (22). There is intermediate reliability evidence that diuretics prevent major cardiovascular events and congestive heart failure more than CCBs do for the management of hypertension. There is evidence that suggests with low to moderate certainty that CCBs are more likely than beta-blockers to reduce major cardiovascular events. Evidence with a low to high degree of certainty indicates that CCBs increased congestive heart failure when compared to ACE inhibitors and ARBs but decreased myocardial infarction and stroke when compared to ACE inhibitors and ACE inhibitors. There is a need for more carefully crafted randomized clinical trials that compare the mortality and morbidity of people on CCBs to people receiving other antihypertensive drug classes in patients with various stages of hypertension, at various ages, and with various comorbidities including diabetes (23).

Complications of CCB

The three primary calcium antagonist medications, verapamil, diltiazem, and nifedipine, have all been linked to severe hypotension. Nifedipine is more frequently associated with tachycardia, headaches, and flushing, while verapamil and diltiazem are more frequently associated with conduction abnormalities and bradycardia. Verapamil generally results in constipation, although nifedipine is known to cause diarrhoea in some cases. Although they are uncommon, idiosyncratic side effects have been noted in the central nervous system, liver, musculoskeletal system, skin, and mouth. Urticarial rashes, gingival hyperplasia, arthralgia, hepatotoxicity, and transitory mental disorientation or akathisia are some of these side effects. Although it has been observed that verapamil, diltiazem, and potentially even nifedipine raise serum digoxin concentrations, it is unclear how clinically significant these medication interactions are. Furthermore, beta-adrenergic blocking medications may be

enhanced by verapamil and diltiazem, and neuromuscular blocking medications may be enhanced by verapamil (24). Peripheral edema development is one of the primary clinical side effects of first and second generation CCBs, including amlodipine. Although, the combination of CCB and a renin-angiotensin system blocker can significantly lower the risk of leg edema (17).

However, CCBs are associated with a modest risk increase for myocardial infarction and heart failure in mixed study populations compared to other active treatments; however, for cardiovascular mortality, there is a very less and negligible trend to a risk increase, and total mortality is similar. The evidence indicates that CCB use is moderately related with an increase in cardiac endpoints among diabetic individuals, particularly when compared to ACE inhibitors. ACE inhibitors are thus preferred as first-line medications among patients with diabetes and those who have heart failure; however, there is no strong evidence to support the superiority of long-acting dihydropyridine or non-dihydropyridine CCBs over other BP-lowering medications among the vast majority of patients who do not have these conditions. The patients' preferences, expected tolerability, and financial considerations can all be taken into account when selecting BP-lowering drug (25).

Shields stated in his study that all types of CCBs have a strong correlation with incident heart failure; this correlation is seen in people with and without pre-existing myocardial dysfunction; BP measurement alone is not a reliable indicator of end organ preservation with CCB use; and CCB-induced heart failure is more problematic in people with comorbid coronary disease, renal disease, and diabetes mellitus. Furthermore, current research suggests that these outcomes are caused by sustained CCB-generated nitric oxide production that causes tissue destruction and inflammation, CCB-induced neurohormonal sympathetic activation, and/or increased systemic calcification as a result of concurrent calcium supplementation. This points to the urgent need for a re-evaluation of CCBs as first-line hypertension treatment options (26). Further research including clinical trials and case-control studies are needed to elaborately study the efficacy of CCB in comparison to other antihypertensive medication since the available literature is scarce and limited to past times.

Conclusion:

CCBs have proven to considerably enhance management of hypertension in monotherapy as well as combination therapy and when there is a favourable tolerability profile. When

administered in combination therapy lesser side effects are reported. More research including recent CCBs in the future is needed to signify the importance**.**

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