Calcium channel blockers (CCBs) are among the most often prescribed drugs for the treatment of hypertension, but there is still uncertainty regarding the risks and benefits of their use as first-line drugs in the treatment of hypertension. Compared with placebo, dihydropyridine CCBs (long-acting nifedipine and nitrendipine) reduce the risk for cardiovascular endpoints, and in a pooled analysis of available studies on treatment of hypertension, significantly decrease the risk for strokes and cardiovascular and total mortality. This also holds true for patients with diabetes who have a clearly reduced risk when treated with CCBs as compared with placebo. However, compared with other active treatments in mixed study populations, CCBs are associated with a small risk increase for myocardial infarction and heart failure, but for cardiovascular mortality, there is only a very small and nonsignificant trend to a risk increase, and total mortality is similar. Among patients with diabetes, compared with angiotensin-converting enzyme inhibitors in particular, available data suggest that CCB use is associated with a moderate increase in cardiac endpoints. Therefore, among patients with diabetes and those with heart failure, angiotensin-converting enzyme inhibitors are preferable as first-line drugs; among the large fraction of patients without these conditions, there is no convincing evidence that long-acting dihydropyridine or nondihydropyridine CCBs are inferior to other blood pressure-lowering drugs. In these patients, the choice of blood pressure-lowering medication can be based on the expected tolerability, costs, and personal preferences. *(Muntwyler J, et al. 2001)*

**Limitations of Amlodipine**

Calcium channel blocker (CCB)-related edema is quite common in clinical practice and can effectively deter a clinician from continued prescription of these drugs. Its etiology relates to a decrease in arteriolar resistance that goes unmatched in the venous circulation. This disproportionate change in resistance increases hydrostatic pressures in the precapillary circulation and permits fluid shifts into the interstitial compartment. CCB-related edema is more common in women and relates to upright posture, age, and the choice and dose of the CCB. Once present it can be slow to resolve without intervention. Peripheral edema is an uncommon problem in patients with untreated hypertension because local autoregulation by smooth muscle components of pre-capillary sphincters protects the capillary bed from increased systemic arterial...
The onset of persistent peripheral edema in a hypertensive patient should trigger a series of diagnostic considerations, albeit rational ones, to minimize a patient's exposure to unnecessary tests as well as to contain costs. In most cases the diagnostic work-up attempts to identify functional abnormalities in the liver, heart, or kidneys. Without definitive findings in these organ systems, a fail-safe diagnosis is peripheral venous insufficiency, although this should always remain a diagnosis of exclusion.

The frequency with which CCB treatment is accompanied by peripheral edema is both compound-specific and dose-dependent. Therefore, a more potent CCB like amlodipine will be associated with higher rates of edema development than a somewhat lower-potency CCB like diltiazem. Reported frequency rates for peripheral edema with CCB therapy are quite varied in the literature in part because of the dose-dependent nature of the phenomenon, and can range from 5% to as high as 70%. (Sica DA. 2012)

**S-Amlodipine – Place in therapy**

Among the calcium channel blockers (CCBs), Amlodipine has an outstanding pharmacokinetic and pharmacodynamic profile. Amlodipine is a racemic mixture, composed of S and R enantiomers in equal proportion. But the calcium channel-blocking activity is confined only to S-amlodipine; R-amlodipine being 1000-fold less active than its S-counterpart. Studies in spontaneously hypertensive rats have shown that R-amlodipine does not lower the blood pressure at all while S-amlodipine lowers the blood pressure effectively. The R-enantiomer which is inactive as a calcium channel blocker thus constitutes an impurity and causes an increased metabolic load on the body when racemic Amlodipine is used in clinical practice.

Further, S-Amlodipine has less pharmacokinetic variability and longer duration of action than the racemate. A pharmacokinetic study of Amlodipine after single oral administrations of 20 mg racemic Amlodipine to 18 healthy volunteers demonstrated that oral clearance of S-Amlodipine is subjected to much less inter-subject variation than that of the R-enantiomer with coefficient of variations of 25% and 52% for clearance of S and R enantiomers respectively.

R-Amlodipine is more rapidly eliminated from plasma than S-Amlodipine, with mean terminal half-lives of 34.9 hours (R) and 49.6 hours (S). Thus the attribute of long duration of action of Amlodipine is dependent on its S-enantiomer. Use of S-Amlodipine alone will thus provide a further longer duration of action than the racemate. S-Amlodipine maintains rather
reinforces the pharmacokinetic advantages of amlodipine (higher bioavailability, longer half-life, lipophilicity, vascular selectivity etc). (Bhandari P, et al. 2012)