REVIEW ARTICLE

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# How Safe are Short Acting Calcium Channel Blockers in Hypertension?

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**The controversies surrounding the use of short acting calcium channel blockers in hypertension are discussed. Much of the controversy has been generated by the study conducted by Psaty *et al*[1]. The study concluded that the use of calcium channel blockers was associated with a 58% to 70% increased risk of suffering from myocardial infarction than with diuretics. In another trial named Appropriate Blood Pressure Control in Diabetes (ABCD), which compared nisoldipine and enalapril, was stopped early because of an excess of myocardial infarction (MI) amongst the patients taking calcium channel blockers (CCB). However amlodipine, a long acting CCB has shown to be beneficial in hypertension and has been widely prescribed. Based on the implications and limitations of the data available for the treatment of hypertension, suggestions were given for the selection of a suitable regimen.**

Calcium channel blockers (CCBs), especially the short acting ones, have been widely prescribed as antihypertensives to patients with essential hypertension in our country. However, the role and safety of CCBs in the treatment of hypertension has not been conclusively established using clinical endpoints (such as mortality, reduced incidence of stroke and myocardial infarction). Controversies on their usefulness have been generated[1]. The Joint National Committee's Sixth Report on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommends diuretics and beta-blockers as the first line agents for the pharmacologic management of hypertension[2]. The recommendations are based on the weight of several large Randomised Controlled Trials (RCT) that consistently show diuretics and beta-blockers reduce mortality and morbidity[2].

## Relevance of surrogate markers:

Only for β-blockers and diuretics conclusive evidence for clinical end points are available[2]. CCBs, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, α-blockers are approved for management of hypertension based on the results of trials showing benefit with a surrogate marker, reduction of blood pressure. Use of surrogate markers to assess long term or chronic therapy has limitations[3]. First, evidence to support efficacy with surrogate markers is generated from studies that are usually of insufficient size and duration to assess safety of the agent. It is important to note that there are no surrogate markers for safety. Studies with a large number of patients conducted over a long period of time (e.g., several thousands of patients, followed for several years) are essential to fully evaluate the safety and efficacy of long term. Second, the reliability of a surrogate marker is based on the strength of association between the marker and clinical outcomes. There are several examples in the cardiology literature of the danger of basing therapy decisions on such associations[4].

## Controversy surrounding the use of calcium channel blockers:

The role and safety of CCBs in treatment of hypertension has been the topic of much controversy over the last few years. Much of the controversy has been

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generated by the study conducted by Psaty *et al*[1]. In this large observational study, the records of 623 cases (those with MI) and 2023 controls (those with out MI), were reviewed. Retrospective data of these patients were reviewed for 30 to 60 d prior to the occurence of MI. When compared to diuretic use, the use of CCBs was associated with a 58 to 70% increased risk of suffering a myocardial infarction. Similar results were obtained when CCBs were compared with beta-blockers. Even though the increased risk appeared to be similar amongst the three classes of CCBs in the study, later studies that examined the CCBs separately found that the short-acting formulation of nifedipine may be associated with an increased risk of reinfarction or death. A meta-analysis of nifedipine trials in secondary prevention suggested a dose response relationship with higher doses of the short-acting formulations associated with a higher mortality in patients with MI, unstable or stable angina[5]. These effects were not seen in patients receiving verapamil or diltiazem.

**Strength of the evidence for harm associated with calcium channel blockers:**

Case control studies as designed by Psaty *et al.*, are not capable of controlling all confounding factors, both unknown and known[1]. Despite their weak ability to prove 'cause-and-effect' relationships, observational studies such as case-control studies help to raise suspicion of adverse events. RCT offer the strongest study design as they evenly distribute confounding factors (both known and unknown) between groups and thus reduce their influence on the outcome. As of today, we do not have enough evidence from such trials. There is one published RCT to date, evaluating the long-term efficacy of a long-acting formulation of nifedipine on clinical events[6]. The study was conducted on 1632 elderly patients followed for a mean of 30 mo and was placebo controlled. Compared to those who received placebo, patients who received long-acting nifedipine had a significantly lower risk of stroke (Relative risk [RR] 0.43, 95% Confidence interval [CI] 0.24-0.77) and cardiovascular events defined as congestive heart failure, MI, severe arrhythmia and sudden death (RR 0.4, 95% CI 0.25-0.64). Also, there was no increased risk of myocardial infarction observed with nifedipine treatment.

In the Systolic Hypertension in Europe (Syst-Eur) trial, the long acting drug nitrendipine reduced the incidence of stroke and a favourable trend was noted in the incidence of myocardial infarction[7]. On the other hand, the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, which compared nisoldipine and enalapril, was stopped early. This was because of an excess of myocardial infarctions (25 vs 5) amongst the patients taking the CCB[2,8]. In the study published by Kloner *et al.*,[9] the all-cause death rate for CCBs were found to be 23.8/1,000 patient years, (p=0.015) whereas the all-cause death for amlodipine in comparative trials was 4.1/1,000 patient-years. This may suggest that amlodipine may have lower risk of death or cardiovascular events when compared with other CCBs in hypertensive patients[9]. Several RCTs are currently underway to evaluate the outcome of morbidity and mortality with long acting formulations and non-dihydropyridine CCBs. The results of these trials may help to resolve the controversy surrounding the CCBs. Currently, CCBs are recommended for use in coronary spasm and in stable angina and hypertension. Also immediate release nifedipine capsules are not indicated for the management of essential hypertension, nor are they recommended for acute reduction of blood pressure.

**Suggestions:**

Based on the implications and limitations of the available data for the treatment of hypertension, the following points may be considered in the care for patients with hypertension:

- Treatment with any antihypertensive agent should only be considered where potential benefit outweighs potential risk. At the same time, since the treatment of hypertension offers conclusive evidence of benefits in clinical endpoints, treatment with an antihypertensive agent is better than no treatment at all.
- The WHO and ISH guidelines published after the JNC VI, clearly state that six classes of drugs can be used as first line agents in hypertension including diuretics, beta-blockers, calcium channel blockers and ACE inhibitors. However, in patients without other co-morbidities, diuretics and beta-blockers remain the first-line therapies, based upon the strong RCT evidence for efficacy on clinical endpoints.
- The risks and benefits of treatment in patients with mild to moderate hypertension are so finely balanced that it is necessary to select the drug for treatment very carefully to minimise withdrawal rate.

- The calcium channel blocker most strongly implicated with a potential adverse cardiovascular outcome is short-acting nifedipine, which has never been indicated for the treatment of hypertension. It is unlikely (although long-term safety has not been documented) that other calcium channel blockers have the same adverse effects. For patients receiving short-acting nifedipine for hypertension, it would seem prudent to change the antihypertensive therapy. If a CCB is preferred, it may be better to use a long-acting CCB like amlodipine, which has proved to be better than other CCBs.

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