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Clinical Trial Experience Around the Globe: Focus on Calcium-Channel Blockers

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Summary: Although certain classes of drugs appear to possess benefits apart from their blood-pressure lowering capability, reduction of blood pressure remains the single most important action of antihypertensive therapy. Calcium-channel blockers (CCBs) have long been recognized as potent agents for hypertension therapy. This is especially true for the prevention of stroke in hypertensive patients as evidenced from the Systolic Hypertension in Europe (Syst-Eur) and Systolic Hypertension in China (Syst-China) trials with a long acting dihydropyridine CCB. The same can be said for beta blockers in patients post myocardial infarction. However, most recent clinical trials have underscored the necessity of multiple drug therapy to achieve the goals of blood pressure reduction coupled with outcomes reduction. For example, the many recent large-scale clinical trials have required an average of three or more agents to achieve goal. Thus, the paradigm for hypertension management has been altered to determine the best treatment regimen rather than the best initial agent. While response rates to individual agents across a wide spectrum of patients vary little, not all drugs are equally suited as companion products. In this article, we discuss the most recent outcome trials with the long acting CCBs alone or in combination with other drugs. The evidence shows that calcium antagonists remain an important part of hypertension management, including in those individuals at risk of cardiac and cerebrovascular events.

Key words: calcium antagonists, clinical trials, drug safety, outcomes research, cardiovascular events

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Calcium Antagonist Controversy

Calcium antagonists and controversy have long been synonymous, particularly in the early and mid 1990s. Numerous case-controlled studies,[1, 2] review articles,[3, 4] and meta-analyses,[5, 6] but few well-designed, double-blind studies were available at that period to establish clearly whether this class of agents was safe and what cardiovascular endpoints were influenced by calcium antagonist treatment. Unquestionably, this led to confusion and concerns on the part of physicians and patients alike. Fortunately, recent years have seen the completion of a number of prospective, randomized, and controlled studies that have enabled physicians to make more evidence-based decisions about the appropriate use of this class of potent blood pressure-lowering agents.[7–12] This article will focus on these studies, along with several meta-analyses[13–15] that help put to rest much of the controversy on the safety of calcium antagonist therapy.

Recent Calcium-Channel Blocker Trials and Analyses

After publication of retrospective case control studies in the mid 1990s created fear and even panic among patients and practicing physicians, by 1996 the controversy quieted and use of the class continued for the treatment of hypertension. However, following the 1998 publication of the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the controversy resumed when it was suggested that the calcium antagonist nisoldipine might increase myocardial infarction (MI) rates in patients with diabetes.[16, 17] It is noteworthy that a long-term follow-up of a subgroup of normotensive diabetic patients in the ABCD trial in 2002 failed to demonstrate a lingering adverse effect associated with calcium-channel blockers (CCBs).[18] With aggressive or intensive therapy, patients did as well on a calcium antagonist-based therapy as on angiotensin-converting enzyme (ACE) inhibitor-based therapy. In fact, the original objective of this trial was to evaluate the importance of the intensity of blood pressure lowering with either drug. More intensive blood pressure control (~128/75 mmHg) was associated with fewer patients progressing from normoalbuminuria

to microalbuminuria (p = 0.028) and microalbuminuria to overt albuminuria (p = 0.028), less progression of diabetic retinopathy, and a lower incidence of strokes.[18]

Clearly we have learned that clinical research with long-term follow-up may yield more convincing data than small, short-term, and often inadequately controlled studies. Before sweeping statements are made regarding the use of any class of agent in any particular subgroup of patients, first there should be careful and systematic approaches to examine the evidence from a variety of clinical trials. In particular subsets of patients, we now have an array of CCB trials that have been published or presented over the last 3 to 5 years (Table I).[7–10] These give practicing physicians better guidance as to how and when to utilize calcium antagonists appropriately in patients with hypertension.

Perhaps the most informative studies of calcium antagonists in patients with hypertension have been the Systolic Hypertension in Europe (Syst-Eur) trial,[7] the Systolic Hypertension in China (Syst-China) trial,[8] and the Nordic Diltiazem (NORDIL) trial.[10] These studies, as well as three meta-analyses that collectively group data from very large studies as well as data from some smaller trials, help put some of the controversy to rest.[13–15]

A subgroup of patients that has received extensive scrutiny is the hypertensive patient who also has type 2 diabetes mellitus. As demonstrated in the Framingham study, diabetes has been identified as the most potent independent risk factor for the occurrence of cardiovascular events.[19] This group of patients often has metabolic abnormalities associated with insulin sensitivity and glucose control, as well as renal dysfunction that can lead to the need for dialysis or renal transplant. However, a real concern is the substantially increased risk of cardiovascular events such as stroke, MI, and sudden cardiovascular death. For nearly 80% of diabetic patients with hypertension, a cardiovascular event is a near certainty, and the life-ending event is often the first and last indication of a hidden cardiovascular problem.[20]

In the Syst-Eur trial—a calcium antagonist-based trial in elderly patients (≥ 60 years; n = 4,695) with isolated systolic hypertension—there was a subset of 492 diabetic patients who were compared with 4,203 nondiabetic patients for further evaluation of the effects of nitrendipine versus placebo.[21] Subjects had the possibility of adding a converting enzyme inhibitor or a diuretic to the therapeutic regimen. While there was a significant 26% reduction in all cardiovascular endpoints in the nondiabetic patient population all endpoints were reduced much more dramatically in the diabetic patient population (69% reduction).[21] These results are consistent with other studies in diabetic patients with hypertension, as this population of patients is characterized by a very high cardiovascular event rate.

If the results of the landmark diuretic therapy-based Systolic Hypertension in the Elderly Program (SHEP) trial,[22, 23] consisting of 4,736 patients aged ≥ 60 years studied for 5 years, are compared with the Syst-Eur[21] results, then it can be inferred that the nondiabetic population demonstrated a similar reduction in mortality, cardiovascular endpoints, stroke, and coronary events. However, the results between the diabetic populations are striking. For example, mortality rates were reduced in both studies, but more so in Syst-Eur[21] than in SHEP.[22, 23] The most impressive results demonstrated in Syst-Eur, and perhaps the hallmark of the study, pertained to the reduction of stroke events. While the diuretic-based SHEP antihypertensive treatment regimen reduced the incidence of total stroke by 36%,[23] the nitrendipine-based Syst-Eur reduced total stroke by 73% in the diabetic subgroup.[21] Another novel finding in Syst-Eur was that the calcium antagonist therapy reduced the onset of dementia, which presumably is caused by microvascular disease in the brain, rather than dementia of the Alzheimer type.[24–26] This finding has prompted many of the new clinical trials now underway to include dementia as a new endpoint, treated with various drugs, including the new angiotensin-receptor blockers.

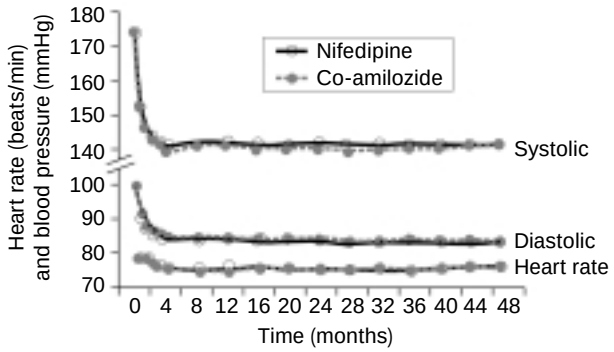
The Syst-China study[8] was modeled after the Syst-Eur study.[7] It had the same background therapy of nitrendipine versus placebo, although a different ACE inhibitor was used. An important difference in these trials was that Syst-China was not a double-blind, randomized trial but rather an open-label design. Nevertheless, event rates among the different cohorts demonstrate that the calcium-antagonist arm reduced total mortality and stroke significantly. In fact, reductions in stroke of 38%[8] were similar to the 42% stroke rate reduction seen in the Syst-Eur trial.[7] Syst-China with 2,394 patients was a smaller study than Syst-Eur, but it did confirm the results of Syst-Eur with dihydropyridine calcium antagonist-based therapy in a different patient population.

The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) trial (n = 6321)

TABLE I Update on calcium-channel blocker outcome trials since the controversy began in early and mid 1990s

Study (Ref. No.)	No. of patients	Study drug	Reference drug
Syst-Eur (7)	4,695	Nitrendipine	Enalapril and hydrochlorothiazide
Syst-China (8)	2,394	Nitrendipine	Captopril or hydrochlorothiazide
INSIGHT (9)	6,321	Nifedipine GITS	Amiloride and hydrochlorothiazide
NORDIL (10)	10,881	Diltiazem	Diuretic and beta blocker

Abbreviations: GITS = gastrointestinal therapeutic system, INSIGHT = International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment, NORDIL = Nordic Diltiazem trial, Syst-China = Systolic Hypertension in China trial, Syst-Eur = Systolic Hypertension in Europe trial.



Patients remaining on treatment

Month	0	4	12	24	36	48
Nifedipine (n)	3157	2735	2498	2234	2058	831
Monotherapy (%)	72	68	66	63	69	
Blood pressure controlled (%)	56	54	54	56	58	
Co-amilozide (n)	3164	2877	2693	2469	2288	944
Monotherapy (%)	66	66	65	63	72	
Blood pressure controlled (%)	59	57	59	57	57	

FIG. 1 Changes for systolic pressure, diastolic pressure, and heart rate are shown for the two treatment groups with nifedipine and co-amilozide (amiloride and hydrochlorothiazide). Adapted from Ref. No. 9 with permission.

utilized a different active comparator calcium antagonist, nifedipine 30 mg, in a long-acting gastrointestinal-transport system (GITS) formulation.[9] It was compared with a potassium-sparing diuretic (amiloride 2.5 mg and hydrochlorothiazide 25 μg) in older patients (aged 55–80 years). Not surprising, most had cardiovascular comorbidities, including a subgroup of diabetic patients who comprised 20% of the population. Figure 1 shows the changes for systolic pressure, diastolic pressure, and heart rate for the two treatment groups in INSIGHT. Blood pressure control was similar in the two groups, with both reducing systolic pressure by almost 30 mmHg and diastolic pressure by about 15 mmHg. The groups also fared similarly with respect to the primary endpoints of MI, stroke, and cardiovascular death over the course of the study. At the end of up to 4 years of exposure, the majority of patients were on monotherapy, which is not typical of most trials today but is a characteristic of SHEP[22, 23] and Syst-Eur.[7] Nowadays, most trials, especially those involving diabetic patients, employ multiple drug regimens, while monotherapy issues are more focused on initial therapy and the degree of blood pressure lowering than in absolute comparisons of individual agents.

Another important trial involving calcium-antagonist therapy was the NORDIL study.[10] This was also an open-label trial; however, it used what is known as the PROBE (prospective, randomized, open, blinded endpoint) design. An endpoint committee, blinded to the treatment randomization group evaluated each MI, stroke, and death. NORDIL utilized diltiazem versus a diuretic or beta blocker or combinations of so-called conventional therapy. Almost 11,000 patients, aged from 50 to 74 years, who had a diastolic blood pressure of ≥ 100 mm Hg were enrolled in the NORDIL trial.[10] With nearly 800 recorded events, diltiazem actually was not as effective in reducing systolic blood pressure as was the reduction in the conventional therapy cohort by about 3 mmHg, whereas the diastolic blood pressure was similar between the two treatment groups. Yet, for the primary endpoint of acute MI, stroke, and cardiovascular death, the point estimate was virtually the same for the two treatment groups. Thus, there was no advantage or lack of advantage for diltiazem versus the beta blockers or diuretics, despite the small difference in systolic blood pressure. On the other hand, there was a significant reduction in stroke in the diltiazem group (n = 159) versus the beta blocker and diuretic group (n = 196). Conversely, the MI rate was 18% higher in the diltiazem group (n = 183) than in the beta blocker and diuretic group (n = 157); this did not achieve statistical significance because of the widened confidence intervals associated with smaller numbers of events and patients. These findings actually create confusion for clinicians because, as in most of the calcium antagonist studies, individually and/or in meta-analyses, CCBs have been better protectors against stroke but conventional therapy has been somewhat better for preventing MIs.

Meta-Analyses Involving Calcium-Antagonist Therapy

Meta-analyses are important because they increase the power of endpoint event rates. Thus, instead of 300 events in one treatment group and 300 in another particular trial, thousands of events can be compared by pooling data from comparable trials.

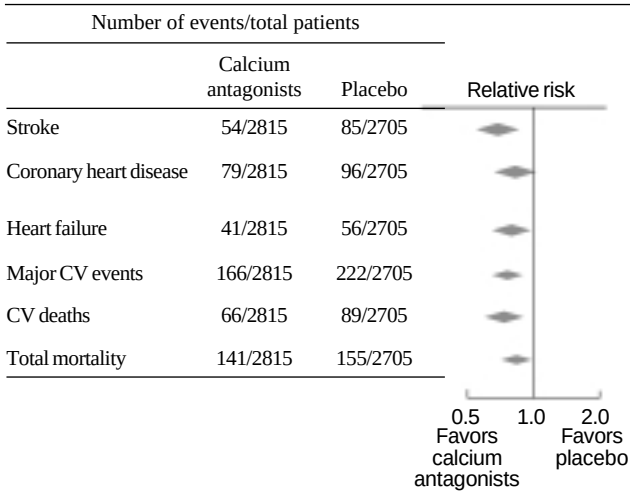


FIG. 2 A meta-analysis comparing calcium antagonist-based therapy with placebo on overall events. CV = cardiovascular. Adapted from Ref. No. 13 with permission.

In a meta-analysis by Neal *et al.*,[13] 17 studies were included with 75,924 patients (mean age 62 years); all of these studies compared active treatment versus placebo or compared a new treatment, such as a calcium antagonist, versus a comparator drug class, such as a diuretic beta blocker, or ACE inhibitor. In the comparison of calcium antagonist versus placebo, the meta-analysis demonstrated a relative risk reduction of 39% for stroke, about 15 to 28% for coronary disease, heart failure, major cardiovascular events, and overall benefit even for all-cause total mortality (Fig. 2).[13]

These data clarify that CCBs are not responsible for an increase in events and, in fact, protect people against events. Even when calcium antagonists are compared with ACE inhibitors, the relative risk reduction for most events is very similar, with the exception of coronary disease and heart failure, where there is a small benefit in favor of the ACE inhibitors. No overall difference in mortality was observed.

In another meta-analysis, Opie and Schall[15] studied six trials with 45,933 patients. They compared the safety of CCBs with either conventional therapy, defined as either diuretics or beta blockers, or in a separate analysis against ACE inhibitors. Against conventional therapy, the CCBs demonstrated a substantial benefit with regard to nonfatal stroke (25% reduction, $p = 0.001$), a detriment to MI of 19% ($p = 0.011$), and no difference with regard to heart failure.[15] All other endpoints, including major cardiovascular events and mortality, were similar.

The CCB analysis versus ACE inhibitors showed no differences between the two treatment regimens with respect to total and cardiovascular mortality. In the subset of diabetic patients, the CCBs had a higher risk of nonfatal (relative risk [RR] = 2.259) and total MI (RR = 2.204).[15] Opie and Schall concluded that ". . . CCBs appeared to be safe and effective when compared to conventional therapy, defined as initiation of therapy with either a diuretic or β-blocker."[15] Calcium-channel blockers also showed comparable safety with ACE inhibitors, except in the treatment of diabetic patients.

Staessen *et al.*'s[14] meta-analysis included nine trials with 62,605 patients with isolated systolic hypertension. The investigators examined the outcomes of patients on newer drugs (e.g., CCBs, ACE inhibitors, or doxazosin) versus older drugs (e.g., diuretics or beta blockers), compared with their expected outcomes based on blood pressure effects. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), for example, doxazosin had a 19% increase in stroke events compared with the reference treatment chlorthalidone.[27] Conversely, based on blood pressure control rates, the Captopril Prevention Project (CAPPP) study would have predicted that conventional therapy reduced event rates to a greater degree than the ACE inhibitor, but captopril yielded better results than expected.[28] In NORDIL, the 3 mmHg difference in blood pressure control mentioned previously would have predicted a 25% increase in events on diltiazem compared with conventional therapy, yet it was closer to 10% because of the significant reduction in stroke associated with diltiazem treatment.[10] The reduction in event rates seen with both older and newer therapies is largely explained by decreases in blood pressure and, although it was theorized that in the Heart Outcomes Prevention Evaluation (HOPE) trial[29] and in the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) trial[11] there may have been an added benefit over and above the blood pressure effect, this hypothesis remains unproven. In fact, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[30] showed quite the opposite. In RENAAL, over 70% of patients were on CCBs as additive therapy to those in the losartan or placebo groups.[11] Thus, patients treated with losartan and conventional therapy, consisting predominately of CCBs, had a reduced overall risk of doubling of serum creatinine, end-stage renal disease events, or death.[11]

Conclusion

Since 1996, numerous trials have demonstrated that calcium antagonists are safe and effective agents for preventing cardiovascular disease in patients with hypertension. Meta-analyses suggest that stroke reduction by treatment with calcium antagonists may be greater not only than treatment with placebo, but also with conventional therapy that includes diuretics and beta blockers. Conversely, ACE inhibitors appear to be superior to calcium antagonists for the prevention of heart failure in patients with hypertension.

These findings support the use of calcium antagonists as an initial therapy in many types of patients with essential hypertension and as a critical part of combination therapy in many patients with comorbidities in whom blood pressure control at more aggressive goals has been deemed essential but remains an elusive target. Future studies will be less focused on comparing one drug against another; rather, they will be based on a multiple drug regimen with known additive blood pressure benefits, and will examine the drugs' effects on complementary, nonpressure-related features that may influence favorable outcomes on renal function, metabolic balance, and neurohumoral control. By building upon our existing knowledge of the benefits of individual agents such as calcium antagonists, these future studies will guide us toward therapeutic combinations that effectively reduce the incidence of cardiovascular, renovascular, and cerebrovascular events.

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