Calcium Antagonists
Effects on Cardio-Renal Risk in Hypertensive Patients
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Abstract—Calcium antagonists comprise 2 main subclasses, dihydropyridines and nondihydropyridines, and have been studied extensively in hypertensive patients. Early meta-analyses suggested that short-acting calcium antagonists were associated with higher mortality rates resulting from cardiovascular events and other etiologies. Recent meta-analyses failed to show any substantive difference between long acting calcium antagonists and other antihypertensive drug classes with regard to cardiovascular outcomes in those with low to moderate cardiovascular risk or kidney disease progression among those with stage 2 or 3 nonproteinuric kidney diseases. The data from calcium antagonist trials are consistent in that they decrease stroke incidence but fail to protect against new-onset heart failure. In people with proteinuric kidney disease, that is >300 mg protein/gram creatinine, use of dihydropyridine calcium antagonists to lower blood pressure without the use of agents that block the renin angiotensin aldosterone system does not provide optimal slowing of nephropathy progression. This relates directly to lack of antiproteinuric effects with this subclass and not seen with nondihydropyridine agents that reduce proteinuria to a greater degree than dihydropyridines. Thus, calcium antagonists are safe and as efficacious as other antihypertensive agents to reduce cardiovascular risk. They should be avoided in people with systolic dysfunction but may be used for blood pressure lowering in people with preserved systolic function. Dihydropyridine calcium antagonists should only be used in conjunction with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in proteinuric kidney disease because they will not optimally slow kidney function loss in their absence. (Hypertension. 2005;46:637-642.)

Key Words: calcium antagonists ■ cardiovascular risk ■ hypertension ■ renal disease

The aggregate of comparative data with a variety of antihypertensive drug classes, to date, has failed to demonstrate clear superiority in relation to overall cardiovascular morbidity and mortality in the management of hypertension in the general population.1–5 Duration of follow-up in these trials, however, limits extrapolation to cohorts that may require such drugs for a decade or longer and relates to concerns about prognostic implications of new-onset diabetes.6,7 The exception to this general conclusion is a reduced incidence of new onset diabetes reported in 12 randomized trials (>100 000 patients), reviewed elsewhere, favoring agents that block the renin-angiotensin-aldosterone system and calcium antagonists over diuretics alone or diuretic–β blocker regimens.7,8 Observational studies as well as some systematic overviews proppor an increased risk for cardiovascular events with the use of some calcium antagonists.9–11 Some of the earlier data primarily addressed the increased cardiovascular risk associated with immediate-release nifedipine, and the hazard in high-risk patient subsets such as patients in the immediate postmyocardial infarction period or those with unstable angina. More recently, conflicting data with long-acting agents in broader patient populations have continued to fuel the controversy.3,12,13

The relationship between choice of antihypertensive agent, blood pressure reduction and renoprotection has also generated considerable controversy. Calcium antagonists lower blood pressure to a comparable degree to other drug classes and slow progression of chronic renal insufficiency. Clear differences exist, however, between calcium antagonists and either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in those with proteinuria.14–16 Various contemporary investigations of calcium antagonist-based antihypertensive therapies have helped shed light on this issue and are discussed in this article.

Classification, Mechanism of Action and Tolerability
Calcium antagonists modulate various calcium-dependent functions of vascular smooth muscle, cardiac myocytes, and the conductive tissues of the heart. Whereas all calcium antagonists share the common feature of inhibiting cellular entry of calcium through voltage-dependent L and T-type calcium channels, significant differences exist between the

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available agents, with regard to binding site and structure. These differences account, in part, for some of the observed clinical differences in dromotropy, negative inotropy, and vascular selectivity.\textsuperscript{17,18}

Nifedipine, diltiazem, and verapamil serve as the prototypic agents for the dihydropyridine, benzodiazepine, and phenylalkylamine classes of calcium antagonists, respectively. The ratio of vascular selectivity to negative inotropy for nifedipine has been estimated at 10:1 and perhaps as high as 1000:1 for certain second-generation dihydropyridine agents, as compared with ratios of 1:1 for diltiazem and verapamil.\textsuperscript{19} Thus, at clinically useful doses, the dihydropyridine calcium antagonists exhibit little to no negative inotropy. Unlike the dihydropyridine calcium antagonists, nondihydropyridine agents exert negative chronotropic effects through interaction with SA nodal and, to an even greater degree, atrio-ventricular (AV) nodal tissues. This latter property renders the nondihydropyridine subclass particularly useful in the management of atrial tachyarrhythmias.

Although all 3 agents have been studied in various patient subsets, long-acting second-generation dihydropyridines such as amlodipine and extended-release preparations of the heart rate-reducing non-dihydropyridine calcium antagonists are most often used in antihypertensive therapy. Agents in both subclasses have the potential to increase myocardial oxygen supply through coronary dilation and prevention of constriction (spasm or endothelial dysfunction). All of these agents reduce myocardial oxygen demand by reducing left ventricular wall stress as a result of the decrease in systolic blood pressure. Consequently, calcium antagonists are effective for relief of all types of angina pectoris including the management of vasospastic (Prinzmetal) angina.

Overall, calcium antagonists are well tolerated by the general hypertensive population. Side effects common to all calcium antagonists include hypotension, flushing, pedal edema, and headache. Hypotension may be particularly pronounced with immediate-release preparations of dihydropyridine agents, such as nifedipine, and angina may be aggravated by the resultant sympathetic activation and reflex tachycardia, which increase myocardial oxygen demands.\textsuperscript{20,21} The hypotension may be more pronounced when the immediate-release dihydropyridine preparations are administered to patients receiving a \(\beta\) blocker, which limits the reflex sympathetic activation. Such pronounced and rapid blood pressure changes are usually not seen with slow-release, long-acting dihydropyridine preparations. In contrast, side effects of nondihydropyridine calcium antagonists can be related to their AV nodal and sinoatrial calcium channel blocking properties and negative inotropy. These side effects may be particularly challenging in patients with sinus node dysfunction who do not have electronic pacers. Bradycardia and side effects of the nondihydropyridine calcium antagonists may also be potentiated by coadministration of \(\beta\) blockers or digoxin, as well as clonidine, propafenone, amiodarone, and other agents that slow the heart rate or influence sinus node function.

The known issues of negative inotropy and pedal edema render calcium antagonists, as a class, undesirable for use in most patients with known left ventricular \textit{systolic} dysfunction with or without overt manifestations of heart failure. One caveat, however, is the use of the second generation dihydropyridine calcium antagonists, amlodipine and felodipine, that have been evaluated in selected groups of patients with stable (class III-IV) chronic heart failure.\textsuperscript{22,23} Although these specific agents were safe in 2 heart failure outcome trials, they did not confer mortality or morbidity benefits seen with ACE inhibitors, angiotensin-receptor blockers, and certain \(\beta\) blockers.\textsuperscript{24,25} Their use in this patient population is, therefore, limited to the capacity of an adjunct antihypertensive or antianginal agent when standard agents are either poorly tolerated or fail to provide adequate blood pressure reduction or angina control despite optimization or dose.

### Cardiovascular Trials and Blood Pressure-Lowering

The efficacy of calcium antagonists with regard to blood pressure control is established from several contemporary randomized clinical trials comparing calcium antagonist-based antihypertensive regimens versus active controls.\textsuperscript{3} The single largest prospective antihypertensive trial, the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), randomized 33 357 hypertensive patients older then 55 years with one additional cardiac risk factor to 1 of 4 initial therapies: chlorthalidone, lisinopril, amlodipine, or doxazosin, with predefined stepped therapies implemented for hypertension control. Whereas the doxazosin arm (\(\sim 9000\) patients) was terminated prematurely because of an excess of cardiovascular events and heart failure admissions as compared with chlorthalidone, the remaining 3 treatment groups were followed for a mean of 4.9 years. At the conclusion of the study, no significant differences were found in the primary outcome of fatal coronary heart disease or nonfatal myocardial infarction (MI) between drug groups, however, both mean and absolute blood pressure reduction during follow-up were significantly different. The blood pressure reduction observed in the amlodipine arm was 11.5/9.3 mm Hg as compared with baseline with 39.5\% of patients seen at 5 year follow-up receiving step 2 (atenolol, clonidine, or reserpine) or step 3 (hydralazine) therapies with an average of 1.9\(\pm\)1.0 antihypertensive medications per patient. Of note, systolic blood pressure was lower with chlorthalidone versus amlodipine or lisinopril (\(-0.8\) mm Hg, \(-2.0\) mm Hg, respectively; \(P<0.001\)), with differences approaching 4 to 5 mm Hg within the first year of the trial.\textsuperscript{26}

Although it is difficult to assess the meaning of these differences in this trial, in general, one should consider that because the vessel sees pressure on a continuum, small differences over time may lead to relatively greater vascular injury. How this translates into events is unclear, but one could speculate from the subanalysis of data of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.\textsuperscript{8} This trial compared amlodipine to valsartan on cardiovascular outcomes in 15 245 patients with hypertension and other multiple cardiovascular risk factors. It demonstrated that participants with stage 2 hypertension, previously treated with 2 or more medications had greater blood pressure-lowering with amlodipine (\(-17.3/9.9\) \(\Delta\)mm Hg, amlodipine versus \(-15.2/8.2\) \(\Delta\)mm Hg, valsartan \(P<0.0001\), with the greatest difference achieved within the
first 6 months of the study. A 3- to 4-mm Hg lower systolic pressure in the calcium antagonist group was associated with a lower event rate within the first 6 months of VALUE.27 At the conclusion of the trial, however, no difference in the primary end point was present.

There have been several cardiovascular outcome trials that evaluate the effects of various calcium antagonists to other agents used to lower arterial pressure. In the International VErapamil-trandolapril STudy (INVEST), >22 000 patients with hypertension and coronary artery disease were randomized to either a strategy based on sustained-release verapamil withtrandolapril and hydrochlorothiazide stepped therapies or a regimen based on twice-daily atenolol plus daily hydrochlorothiazide and trandolapril-stepped therapies and followed for a mean of 2.7 years.28 In INVEST, mean blood pressure reduction at 24 months was comparable between arms and there was no difference in the primary outcome (all-cause mortality, nonfatal MI or nonfatal stroke) between the 2 groups at study end. Importantly, in INVEST >50% of patients required 3 or more antihypertensive medications to achieve target blood pressure.

A separate study that compared a non-dihydropyridine calcium antagonist to a β blocker on cardiovascular outcomes in hypertensive patients was the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) Trial. In this trial, 16 602 hypertensive patients with one additional cardiac risk factor were randomized to COER verapamil or a β-blocker (atenolol). Diuretics were strongly suggested as second agents in both groups. Blood pressure was comparably reduced in both with 65.9% of patients in both study groups attaining a blood pressure <140/90 mm Hg after 3 years of follow-up.29

Another large study, The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), compared the effects of a calcium antagonist, amlodipine, against a once-daily β blocker, atenolol, for the prevention of coronary heart disease events in 19 342 hypertensive patients who have no history of coronary heart disease.30 This trial was stopped early by the Data Safety Monitoring Board because of a clear benefit of the calcium antagonist on the primary end point. This trial, like INVEST, used an ACE inhibitor as its add-on agent.30,31 Thus, the available randomized trial data support the efficacy and tolerability of calcium antagonists, as a class, to not only lower blood pressure but also reduce the risk of coronary heart disease events and stroke.3

An earlier trial, the NORdic DIltiazem (NORDIL) study,32 was a prospective randomized open-label blinded end point (PROBE) design that evaluated a much younger group of patients than those discussed in INVEST and VALUE, ie, 10 881 middle-aged patients with a diastolic blood pressure >100 mm Hg. Patients were randomized to either diltiazem, diuretics, β-blockers or the combination of the 2, and titrated to a target diastolic blood pressure <90 mm Hg. Systolic blood pressure reduction in the diuretic/β-blocker group was slightly greater than that observed with calcium antagonist alone (23/19 mm Hg versus. 20/19 mm Hg; P<0.001); however, like other studies, no difference in the primary composite end point of fatal and nonfatal stroke, MI, or cardiovascular death was noted.

Taken together, these studies all demonstrate that effective blood pressure reduction, especially early in the course of treatment as evidenced by the VALUE trial, will lead to fewer events and, hence, better outcomes when using agents with greater efficacy. Relevant to this issue, early consideration of multi-drug regimens is advocated by guidelines, especially in patients with blood pressure elevations above target pressure.1,33 Several large prospective trials have demonstrated that the mean number of agents required for attaining target blood pressure ranged between 2 and 4 agents.14–16,26,28,34,35

**Perceived Safety Issues and Cardiovascular Outcomes**

Calcium antagonists have been available and widely prescribed in the United States for nearly 2 decades. When these agents first appeared, they were short-acting with fairly high side effect profiles and noted to increase the incidence of MI, primarily driven by trial results with nifedipine.10,36 Further controversy ensued after publication of 2 meta-analyses on calcium antagonist use, arriving at seemingly disparate conclusions. In one meta-analysis of nine selected trials (n=27 743), Pahor et al found calcium antagonist use associated with an increased risk of acute MI as well as risk of major cardiovascular events and heart failure compared with other antihypertensive agents but no difference in the risk of stroke or all-cause mortality.13 In contrast, a report from the Blood Pressure Lowering Treatment Trialists’ Collaboration published simultaneously, did not find any evidence for excess risks associated with calcium antagonist use.37 Key differences between the 2 analyses included larger numbers of patients in the latter analysis and comparison of calcium antagonists with active control therapies in the former versus placebo-controlled comparisons in the latter.

Three more recent meta-analyses, one by Staessen et al who analyzed data from 9 randomized trials (n=65 605),4 and a second of an updated analysis by the Blood Pressure Lowering Treatment Trialists’ Collaboration who reported data from 136 124 patients enrolled in 27 trials,3 showed comparable long-term efficacy and safety of calcium antagonists compared with β-blockers and diuretics. The third and most recent and comprehensive analysis evaluated data from 162 341 patients enrolled in 29 randomized trials.5 In this analysis, calcium antagonists were associated with significant reduction in stroke and major cardiovascular events compared with placebo with a modest reduction in coronary heart disease events, a trend toward reduced cardiovascular death but no effect on new onset heart failure. In parallel with earlier meta-analyses, calcium antagonists were associated with a trend toward reduced stroke compared with diuretics or β-blockers.3,4 Note that across all trials that reported fatal outcomes, an increase in fatal MI was noted in only one trial with nifedipine gastrointestinal transfer system (GITS) in the Intervention as a Goal in Hypertensive Treatment (INSIGHT) trial.38

Calcium antagonists are perhaps the most efficacious agents to reduce stroke other than diuretics in older persons. A number of trials including the NORDIL, INSIGHT, Systolic Hypertension in Europe (SYST-EUR), and VALUE, as well as most properly performed meta-analyses, demonstrate efficacy of this class on stroke reduction.4,5,8,32,39,40 One exception to this is the
Progression of Kidney Disease

Blood pressure reduction in early nonproteinuric kidney disease markedly slows progression of nephropathy, regardless of the class of antihypertensive agent used.\(^{34,44,45}\) Prevention of kidney disease progression is critical because renal dysfunction, that is, levels of estimated GFR of <60 mL/min, is a major independent contributor to the development and aggravation of cardiovascular disease.\(^{46,47}\) Whereas cardiovascular mortality attributable to hypertension has steadily declined over the past 2 decades, the incidence of end-stage renal disease in the United States population has continued to increase.\(^{48}\)

Proteinuria accompanying nephropathy may reliably be used as marker of kidney disease progression and as a prognosticator for cardiovascular risk.\(^{49–52}\) Improvement in proteinuria is associated with reduction in cardiovascular events.\(^{50}\) Blood pressure reduction using ACE inhibitors or ARBs, as part of the antihypertensive regimen, is associated with reduction in proteinuria and slowing of nephropathy progression in patients with chronic renal insufficiency.\(^{53,54}\) It remains unclear, however, if calcium antagonists, as a class, offer similar renoprotective benefits.

A systematic review reported by Kloke et al found calcium antagonists effective antihypertensive agents but of uncertain value in patients with proteinuria and elevated creatinine.\(^{55}\) In several prospective randomized trials of people with proteinuric kidney disease, progressive increases in proteinuria and a more rapid decline in kidney function were noted in patients treated with dihydropyridine calcium antagonists versus those treated with ACE inhibitors or ARBs.\(^{14,16}\) In 2 outcome trials, the African-American Study of Kidney Disease (AASK) study and Irbesartan Diabetic Nephropathy Trial (IDNT), the dihydropyridine calcium antagonist, amlodipine, failed to slow decline in kidney function or mitigate against increases in proteinuria in patients with hypertension and proteinuric nephropathy compared with an ACE inhibitor or ARB regimen.\(^{14,16}\) In contrast, several small long-term clinical studies using non-dihydropyridine calcium antagonists have demonstrated reductions in proteinuria and slowed declines in GFR but not end-stage renal disease.\(^{56–59}\)

A recent systematic review of 28 randomized trials evaluating renal outcomes in hypertensive patients with or without diabetes found similar blood pressure-lowering with differential antiproteinuric effects between dihydropyridine and non-dihydropyridine calcium antagonists.\(^{58}\) The primary end point assessed was percentage change in proteinuria, compared with baseline values, in patients treated with one of the calcium antagonist subclasses. Blood pressure data (n=1338) and kidney function data (n=510) were analyzed. Differences in proteinuria reduction between groups (+2% with dihydropyridines versus –3% with non-dihydropyridines; \(P=0.01\)) were noted. After adjustment for blood pressure, sample size and study duration, a trend persisted in favor of proteinuria reduction for the non-dihydropyridines. A secondary analysis supported the benefit of nondihydropyridines with or without concurrent ACE inhibitor or ARB therapy.\(^{59}\) These findings are important because recent data from a \textit{post hoc} analysis of the AASK trial indicate that reduction in proteinuria of \(>50\%\) from baseline, within the first 6 months of therapy, is associated with a much lower 5-year incidence of end-stage renal disease in those with nondiabetic kidney disease.\(^{51}\) This is further bolstered by data on cardiovascular outcomes that showed a similar relationship between reductions in albuminuria and events.\(^{50}\)

An explanation for proteinuria difference within the class come from animal models in which dihydropyridine agents inhibit renal autoregulatory capacity through their effect on the afferent arteriole.\(^{60–62}\) Resultant direct transmission of systemic pressures can lead to glomerular hypertension which, in turn, mediates endothelial damage, fibrosis, increased protein filtration and albuminuria. Nondihydropyridines, in contrast, do not interfere with glomerular autoregulation to the same degree. Nondihydropyridines also reduce glomerular permeability to a greater extent than dihydropyridine agents. This is evidenced in 2 separate prospective studies, one of which was on background ACE inhibitor therapy. In both these studies, dihydropyridine calcium antagonists increased glomerular permeability and had much less proteinuria reduction compared with nondihydropyridine agents.\(^{59,63}\) Although these differences may help explain the differential effects of the 2 subclasses on proteinuria, the only outcome data when used in combination with an ARB come from a subanalysis of the RENAAL trial that demonstrated a similar outcome in the group that received a dihydropyridine calcium antagonist.\(^{64}\)

Summary and Conclusions

Calcium antagonists comprise 2 subclasses, dihydropyridines and nondihydropyridines, which are different with respect to vascular selectivity, negative inotropy, effect on cardiac impulse formation, and conduction, as well as progression of renal dysfunction. Both subclasses appear to offer similar antihypertensive efficacy. The totality of clinical trial data with calcium antagonist-based antihypertensive regimens supports cardiovascular risk reduction comparable to other agents.

This efficacy and safety profile of calcium antagonists has resulted in the JNC 7 and European Hypertension Guidelines supporting their use as initial therapy for those with isolated systolic hypertension especially for stroke reduction and for use as an add-on agent to achieve blood pressure goals in other diseases except for heart failure associated with systolic
dysfunction. In the European guidelines they are 1 of 5 classes suggested for use as first-line therapy. As noted in these guidelines, as well as those of the American College of Cardiology/American Heart Association, this class of agents should ideally be avoided in patients with known left ventricular systolic dysfunction, except possibly class III patients in whom other therapies have failed and need further reduction of blood pressure. They are recommended, however, for those with hypertension and heart failure who have preserved systolic function. Should refractory angina or resistant hypertension necessitate addition of a calcium antagonist in this patient subset, selected second-generation dihydropyridines appear to be safest because these patients will require use of a \( \beta \) blocker.

Differential renoprotective benefit is present with nondihydropyridine agents in the subset of patients with advanced proteinuric kidney disease, because they reduce proteinuria to a greater degree than dihydropyridines, independent of diabetic status. Based on the recommendations of the Kidney Disease Outcomes Quality Initiative Blood Pressure guidelines, nondihydropyridine calcium antagonists alone or in conjunction with an ACE inhibitor or ARB, are preferable in hypertensive patients with proteinuria of >300 mg/d, as well as those with impaired kidney function.

References


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