Arterial Calcification and Calcium Antagonists
What Does It Mean?

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Since their introduction more than 30 years ago, calcium antagonists have emerged as one of the most attractive and widely used classes of antihypertensive agents. Of the 20 to 25 million patients receiving medication for hypertension in the United States, about one quarter are taking calcium antagonists. The wide appeal of the calcium antagonists is attributable to several features, including efficacy in virtually all demographic groups, beneficial characteristics such as metabolic neutrality, and the occurrence of relatively few and primarily nuisance-type side effects. In addition, recent investigations have focused on their possible protective effects on target organs, such as the heart and kidney, further enhancing their value.

Despite these attributes, a number of retrospective analyses have suggested that calcium antagonists may be detrimental and may promote adverse cardiovascular events. On the basis of this and other retrospective analyses, Pahor et al proposed that the use of calcium antagonists as first-line antihypertensive agents should be discontinued.

Although meta-analyses and observational studies clearly have limits, Pahor et al raised an important question that deserves consideration: whether calcium antagonists, as a group, promote adverse cardiovascular events, specifically coronary artery disease. Furthermore, media reporting of the presentation triggered concern among users of calcium antagonists and even among those taking other antihypertensive drug therapies.

Elsewhere in this issue, Motro et al report the results of a study that some have invoked as bearing on this controversy. These investigators attempted to assess the utility of ultra-fast computerized tomography (CT) to determine the difference between 2 drug regimens in slowing the progression of coronary artery calcification. Baseline and serial helical CT scans for coronary artery calcification were made in a subgroup of patients enrolled and randomized for the International Nifedipine Study: Intervention as Goal for Hypertension Therapy (INSIGHT), which compared nifedipine GITS and amiloride-thiazide as primary treatment for hypertension.

A comparison of those patients available for follow-up assessment suggests a greater increase in calcium score for those in the amiloride-thiazide group compared with the nifedipine GITS group; this is most apparent at the end of the first year. A critical evaluation of this study and its experimental approach provides important insights into the vagaries and limitations in the application and extrapolation of fast CT:

- Only a small number of subjects were actually evaluated both at baseline and 3 years. Consequently, this results in a study with only minimal power to discover meaningful outcomes and the problem encountered herein of a "significant" difference at 1 year and 3 years but not at 2 years.
- The criteria selected for study (total calcium scores ≥10) were not apparently prespecified, and the authors do not tell us why that was the score they chose.
- The baseline values are not identical, as might happen in such a small cohort, and consequently, the authors should have expressed the changes they noted in both absolute numbers and in percentages. This might have given us a better idea of the real impact of time and whether the effect of the drugs was really different.
- The actual cohort tested is so far from the original group that the subgroups evaluated are not equivalent. This is recognized by the authors but not elaborated on. Unfortunately, the response to treatment is not reported. Did the group with an increased calcium score respond better (ie, have a lower blood pressure), worse, or the same to 1 of the regimens or to both? This is important information in light of the implied assertion that more calcium in the arteries indicates more atherosclerosis.
- Lastly, and perhaps most importantly, we are not really sure that increasing calcification of the coronaries determined by ultra-fast CT is necessarily a poor prognostic sign. Without other information, one might conclude that calcium score serves as a surrogate end point for outcomes of concern. However, the overall results of INSIGHT are now available and fail to establish superiority for nifedipine GITS. Furthermore, the significantly greater rates of myocardial infarction (relative risk, 3.22) and nonfatal heart failure (relative risk, 2.20) on nifedipine GITS cannot be easily dismissed.

The opinions expressed in this editorial are not necessarily those of the editor or of the American Heart Association.

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Of interest, a large National Institutes of Health–sponsored observational study is currently in progress to attempt to evaluate whether calcium score serves as surrogate end point or outcomes of concern. So many surrogate markers of disease (left ventricular mass, intimal-medial thickness of the carotid arteries, microalbuminuria, and pulse wave velocity) and how they are affected by therapy prove to be interesting but not as useful in determining clinical outcomes as we would like.

Hopefully, these considerations should constitute a caution in interpreting the inevitable flurry of future studies that will attempt to extrapolate differences in calcium score to outcomes of concern. Of equal importance is the pervasive and contentious issue of whether calcium antagonists impact cardiovascular outcomes and whether they should continue to constitute first-line antihypertensive agents. Hopefully, the ongoing Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) will definitely resolve this controversy.9 While we await this answer, several recently available studies, including the diabetic cohort in the Systolic Hypertension in Europe Trial (SYST-Eur)10 and the diabetic cohort in the Swedish Trial in Old Patients with Hypertension–2 (STOP-2),11 strongly suggest that relative risk for cardiovascular end points, including total mortality, and cardiovascular mortality is not increased by the newer generation of long-acting dihydropyridines. Given the magnitude of the problem of hypertension, and the reality that hypertension control rates are substantively poor worldwide, we believe that these newer generation calcium antagonists should continue to constitute part of the antihypertensive armamentarium until definitive proof accrues that they are inferior to other classes of antihypertensives.12

References


Key words: coronary calcification nifedipine co-amilozide computed tomography
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Hypertension. 2001;37:1414-1415
doi: 10.1161/01.HYP.37.6.1414

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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