Calcium Channel Blocker Nifedipine Slows Down Progression of Coronary Calcification in Hypertensive Patients Compared With Diuretics

Michael Motro, Joseph Shemesh

Abstract—Calcium controls numerous events within the vessel wall. Permeability of the endothelium is calcium dependent, as are platelet activation and adhesion, vascular smooth muscle proliferation and migration, and synthesis of fibrous connective tissue. Double-helix computerized tomography is a noninvasive technique that can detect, measure, and compare coronary calcification in the coronary arteries. Using this method, our objective was to determine whether administration of nifedipine once daily in lieu of diuretics in high-risk hypertensive patients will arrest or slow down the progression of coronary artery calcification. The study was designed as a side arm of INSIGHT (International Nifedipine Study: Intervention as Goal for Hypertension Therapy), aimed to show the efficacy of nifedipine once daily versus co-amilozide (hydrochlorothiazide 25 mg, amiloride 2.5 mg) in high-risk hypertensive patients. A total of 201 patients with a total calcium score of ≥10 at the onset of study who underwent an annual double-helix computerized tomography for 3 years were analyzed for efficacy. Inhibition of coronary calcium progression was significant in the nifedipine versus the co-amilozide group during the first year (3.18% versus 27%, respectively, \(P=0.02\)), not significant during the second year (28.5% versus 47%, respectively, \(P=0.14\)), and significant during the third year (40% versus 78%, respectively, \(P=0.02\)). The results point to a slower progression of coronary calcification in hypertensive patients on nifedipine once daily versus co-amilozide. (Hypertension. 2001;37:1410-1413.)

Key Words: coronary calcification ■ nifedipine ■ co-amilozide ■ computed tomography

Atherosclerosis (AS) is a multifactorial disease. Not limited to lipid accumulation, it involves the localized accumulation of collagen, elastin, and calcium, together with monocyte infiltration, endothelial injury, and smooth muscle cell proliferation and migration.\(^1\)\(^-\)\(^5\) Many of these events are calcium dependent and may be affected by calcium antagonists. Although the prevalence of coronary calcification increases with age, pathological studies have consistently shown a direct relation between the degree of calcification and the severity of coronary AS, independent of the patient’s age.\(^6\)\(^-\)\(^7\) The development of fast tomographic scanning techniques provides a noninvasive modality for the detection, quantification, and progression of calcific AS. Using electron beam computed tomography, Callister\(^8\) demonstrated that hypertensive patients who were treated with statins and whose average LDL cholesterol level was ≥120 mg/dL at study onset had a lower increase in coronary calcium volume score than all others.

Our objective was to determine, over a 3-year period, whether the use of nifedipine once daily versus co-amilozide in hypertensive patients at high risk for coronary AS will arrest or slow down the progression of calcifications in the coronary arteries.

Methods

Study Design

The study was designed as a side arm of INSIGHT (International Nifedipine Study: Intervention as Goal for Hypertension Therapy). This prospective, randomized, double-blind trial was performed in Europe and Israel on 6321 hypertensive (blood pressure ≥150/95 mm Hg or systolic blood pressure ≥160 mm Hg) patients age 55 to 80 years with at least 1 of 10 additional cardiovascular risk factors, such as diabetes mellitus or hypercholesterolemia. Through dynamic randomization, patients were assigned to initial treatment with either nifedipine once daily (30 mg) or co-amilozide (hydrochlorothiazide 25 mg, amiloride 2.5 mg), such that similar numbers of patients with each risk factor could be compared between the 2 drugs. Dose titration was principally by dose doubling and addition of atenolol (25 to 50 mg) or enalapril (5 to 10 mg), aiming to compare cardiovascular morbidity and mortality in both. Detailed protocol was reported.\(^9\)

All patients recruited into the main study in 18 centers in our region were asked to volunteer for the side-arm study; those who agreed were enrolled (on signing a consent form) between January 1995 and March 1996. All patients were referred to a single center for coronary double-helix computerized tomography (DHCT). All examinations throughout the study were interpreted by a single physician blinded to the treatment groups.

All patients underwent baseline DHCT on enrollment; patients with a total calcium score (TCS) of ≥10 continued to undergo a DHCT annually for the next 3 years. Patients with a TCS between 0 and 9.9 had 1 final DHCT on study termination.
End point was the comparison of the TCS following the unblinding of the treatment in both arms.

Recruitment
Over a course of 15 months, 547 high-risk hypertensive patients were enrolled into the calcification study INSIGHT, undergoing a baseline coronary DHCT.

Over 3 years, 171 patients dropped out of the main study because of the following: death, myocardial infarction, cerebrovascular accident, angina pectoris, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, edema, headaches, flushes, elevated blood pressure, noncompliance, and insufficient therapeutic effect. Out of the 376 patients who underwent the end-of-study third-year DHCT, 126 had a TCS of 0; 41, a TCS of 0.1 to 9.9. Of 209 patients with TCS of $\geq 10$, 8 were not analyzed because of noncompliance with the time window for DHCT, that is, 1 of their DHCTs was not performed within 6 months of the scheduled date. A total of 201 patients with a TCS $\geq 10$ at study onset who underwent an annual DHCT were analyzed for efficacy.

The VC (Valid for Efficacy) group consisted of patients demonstrating coronary calcification at baseline (ie, TCS $\geq 10$); these underwent annual DHCT for the following 3 years. ITT (Intention to Treat) comprised the entire study population, including patients with a TCS of 0.

DHCT Protocol

**DHCT Determination of Coronary Calcification**
A calcific lesion was defined as an area within a coronary artery with a tomographic density above a threshold of 90 Hounsfield units (HU) $>8$ SD above blood density, covering an area of $\geq 0.5$ mm$^2$ ($>2$ pixels).

Figure 1A and 1B represent examples of markedly significant coronary calcification progression over a 3-year period.

**DHCT Image Acquisition and Quantification of Coronary Calcium**
For DHCT image acquisition and quantification of coronary calcium, see detailed protocol at http://www.hypertensionaha.org.

Statistical Analysis
Taking into account the dispersion of the data and the rather large number of outliers, absolute values are presented as geometric means or median and interquartile ranges. For further analysis, the individual data were log transformed: new = $\log_{10}(\text{old}+0.5)$ so as not to miss the value’s zero. ANCOVA was applied on the delta (end point–baseline). The baseline value was included as a covariate; percentage increase of TCS value is the quotient of the geometric mean of each visit from baseline. ANCOVA with repeated measure was used to obtain multivariate overall comparison for the completers.

The SAS procedure GLM was used for statistical analysis.

Results
Baseline characteristics for both treatment arms are presented in the Table, with gender, age, weight, and height similar in both groups. Although not statistically significant, among the nifedipine arm, there was a higher number of patients with diabetes mellitus, with coronary heart disease, and on aspirin therapy. The ITT population did not differ. The geometric mean of the total (maximum) calcium score for the VC group is presented in Figure 2A. The TCS of patients on co-amiloazide progressed over a 3-year period from 118 to 208, whereas the progression on nifedipine was from 108 to 151.

The total progression in the left anterior descending artery (LAD) was similar at the end of 3 years; the TCS in the co-amiloazide arm was 146 versus 102 in the nifedipine arm (Figure 2B). The median and interquartile range of absolute change in TCS on therapeutic intervention over a 3-year period are presented in Figure 3.

### Baseline Characteristics and Risk Factors (N=202)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nifedipine</th>
<th>Amiloazide*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>62/40</td>
<td>64/36</td>
</tr>
<tr>
<td>Age, yr</td>
<td>67±6</td>
<td>66±6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80±14</td>
<td>77±14</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165±8</td>
<td>165±9</td>
</tr>
<tr>
<td>Duration of hypertension, yr</td>
<td>11.6±8.5</td>
<td>12.9±9.2</td>
</tr>
<tr>
<td>Family history of hypertension, n (%)</td>
<td>35 (34.7)</td>
<td>39 (39)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>17 (16.7)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>37 (36.3)</td>
<td>40 (40)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>31 (30.4)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td>19 (18.6)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>8 (7.8)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>19 (18.6)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Aspirin therapy, n (%)</td>
<td>37 (36.3)</td>
<td>30 (30)</td>
</tr>
</tbody>
</table>

*Amiloazide indicates hydrochlorothiozide/amiloride.
Figure 4 presents the annual increase of TCS in both groups. Inhibition of the calcium progression was significant in the nifedipine versus the co-amilozide group during the first year (3.18% versus 27%, respectively, $P \leq 0.02$), not significant during the second year (28.5% versus 47%, respectively, $P = 0.14$), and significant during the third year (40% versus 78%, respectively, $P \leq 0.02$).

The overall treatment effect of nifedipine demonstrated significant inhibition of coronary calcium progression over 3 years ($P \leq 0.02$).

The ITT population demonstrated a significant difference only at the end of the second year ($P = 0.03$). This difference abated during the third year, because all the patients with a TCS of 0 were included.

**Discussion**

Postmortem studies of excised coronary arteries have demonstrated that coronary calcium is associated with AS and that its quantity reflects the overall extent of coronary AS. These calcified deposits are usually associated with complex atherosclerotic plaques and found to be present in most coronary obstructions on necropsy. In human trials, there are several reports using sequential angiograms that suggest a therapeutic or prophylactic effect of calcium antagonists on the progression of the atherosclerotic process.

The effect of calcium channel blockers as a preventive therapy of the atherosclerotic process was evaluated in the INTACT study using nifedipine, in the Montreal study using nicardipine, and in the PREVENT study using amlodipine. All these studies used consecutive coronary angiography. Although the former 2 studies demonstrated a modest benefit in preventing the progression of new lesions only, the latter revealed no effect whatsoever.

By tracking plaque progression with angiography, a significant amount of information is lost because only the protruding portion of the plaque is demonstrated, which could be a cardinal reason why minor or no changes were found in those studies.

In the PREVENT study, in which intimal medial thickness of the carotid artery was measured directly by using ultrasound, the calcium channel blocker amlodipine was found to inhibit intimal medial progression in type 2 diabetes mellitus.

In this study we chose to track the progression of the calcific atherosclerotic process as a marker of overall AS in the coronary vessels by using DHCT.

The accuracy and reproducibility as well as the diagnostic contribution in various clinical conditions of coronary DHCT have been reported. Using this method to track coronary calcium, we recently reported the mean interstudy variability to be 32%; the current study’s coronary calcification delta increase is 95% (40% versus 78%), well above the variability range.

After 3 years, the total calcium score increase on nifedipine was 40% versus 78% on co-amilozide. The ITT population did not demonstrate a significant difference, mainly because 40% of the patients in that group had no coronary calcification at the onset as well as at the conclusion of the study, a large number which diluted the rest of the group.

The patients who demonstrated calcium at the onset of the study manifested significant slowing of calcium progression on nifedipine.

In light of the results of the main INSIGHT study, which showed equal effectiveness of nifedipine once daily versus co-amilozide in preventing overall cardiovascular or cerebrovascular complications, the clinical implication of our findings is not entirely clear.
Coronary calcium, an unequivocal marker of coronary AS,\textsuperscript{24,25} can be detected and measured by dual–slice spiral computerized tomography.\textsuperscript{17,18} The quantity and extent of coronary calcium and AS are directly related.\textsuperscript{26,27} Although absence of calcium excludes occlusive disease,\textsuperscript{20,28} comparative angiographic studies consistently demonstrate a direct correlation between the TCS and the number of occluded vessels.\textsuperscript{25} This correlation can be clinically applicable to stable angina, a chronic manifestation of coronary artery disease. However, in the most threatening form of coronary artery disease—acute myocardial infarction and unstable angina—the underlying vulnerable plaques are mainly composed of soft lipid and fibrous materials with mild or even without calcium.\textsuperscript{29} The inability of computerized tomography modalities to visualize these soft plaques is the main limitation of the technique, reducing the power of calcium to predict acute events.

Limitations
Although the results of this prospective double-blind side-arm study point toward a possible change in therapeutic concept, the number of participants was not large enough in comparison to a contemporary evidence-based controlled trial. Results of pending studies will determine whether a change in clinical practice is warranted.

In summary, the results point to a slower progression of coronary calcification in patients on nifedipine once daily versus co-amloidos.

Acknowledgments
This work was supported by a grant from Bayer AG, Germany. The authors wish to thank Dr Dan Stolero, of Pharma-Clinical (CRO) Ltd, Israel, for his excellent and diligent monitoring of the study as well as his insightful comments. The excellent technical assistance of Ms. Silla Silverwasser is gratefully noted. Participating investigators were J. Ben-Ari, D. Ben-Ishay, S. Ben-Shitrit, J. Bernheim, S. Botwin, M. Bursztyn, A. Caspi, E. Faran, J. Fidel, F. Glikberg, Y. Goren, E. Grossman, A. Iaina, B. Kristal, S. Oren, J. Rosenfeld, J. Shochat, R. Viskoper, J. Weissgarten, Y. Yagil, D. Zevin, A. Zilberman, and R. Zimlichman.

References
Calcium Channel Blocker Nifedipine Slows Down Progression of Coronary Calcification in Hypertensive Patients Compared With Diuretics
Michael Motro and Joseph Shemesh

Hypertension. 2001;37:1410-1413
doi: 10.1161/01.HYP.37.6.1410

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/37/6/1410

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2001/06/25/37.6.1410.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/