Calcification of the Thoracic Aorta as Detected by Spiral Computed Tomography Among Stable Angina Pectoris Patients
Association With Cardiovascular Events and Death

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Background—Calcification of the thoracic aorta is associated with atherosclerotic risk factors, yet its pathogenesis and clinical implications are not yet elucidated. The goal of the present study was to assess whether thoracic aorta calcification is associated with an increased risk of cardiovascular events and death in patients with stable angina pectoris.

Methods and Results—A prospective cohort of 361 stable angina pectoris patients (307 men, 54 women; age range, 37 to 83 years) underwent chest spiral computed tomography and were evaluated for aortic calcification. We recorded the incidence of cardiovascular events and death during a 4.5- to 6-year follow-up. Aortic calcification was documented in 253 patients (70% of patients; 213 men, 40 women). Patients with aortic calcification were older (mean age, 65±7 versus 55±9 years; \( P<0.001 \)), and fewer were classified as smokers (13% versus 26%; \( P=0.014 \)) compared with patients without aortic calcification. Significant correlation was found between patients with and those without aortic calcification for the presence of aortic valve calcification (28% versus 11%; \( P<0.001 \)), mitral annulus calcification (29% versus 4%; \( P<0.001 \)), and coronary calcification as expressed by coronary calcium score. \( (P<0.001) \). During 4.5 to 6 years of follow-up, 19 patients died, all of whom were in the aortic calcification group. Age-adjusted hazard ratios for total events and cardiovascular events by aortic calcification were 2.84 (95% CI, 1.52 to 5.30; \( P=0.001 \)) and 2.70 (95% CI, 1.33 to 5.47; \( P=0.006 \)), respectively. In multivariable analysis, hazard ratios for total events and cardiovascular events were 2.79 (95% CI, 1.46 to 5.20; \( P=0.002 \)) and 4.65 (95% CI, 1.19 to 18.26; \( P=0.028 \)), respectively.

Conclusions—Calcification of the thoracic aorta is age related and associated with coronary calcification and valvular calcification. Thoracic aortic calcification is associated with an increased risk of death and cardiovascular disease. \((\text{Circulation.} \ 2008;118:1328-1334.)\)

Key Words: angina pectoris ■ aorta ■ atherosclerosis ■ calcification ■ computed tomography
whether thoracic aorta calcification is associated with an increased risk of cardiovascular events and death during a prospective follow-up in a cohort of patients with stable angina pectoris enrolled in a Coronary Disease Trial Investigating Outcome With Nifedipine GITS (ACTION) in Israel.

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Methods

Study Population

This work uses the spiral CT scans of patients with stable angina pectoris who were participating in the ACTION calcification study, a side arm of the main ACTION trial in Israel. ACTION is a multicenter, randomized, placebo-controlled, double-blind trial to compare the effect on clinical outcomes of long-acting nifedipine or placebo in patients with angina pectoris attributable to coronary disease. A detailed description of the main trial has been published previously. In brief, 3 categories of ambulatory patients who were ≥35 years of age, had angina pectoris that had been stable for at least 1 month, and needed oral or transdermal treatment either to treat or to prevent anginal attacks were eligible for the study: (1) those with a history of MI, (2) those with angiographic coronary artery disease but no history of MI, and (3) those with a positive exercise test or perfusion defect who had never had coronary angiography and had no history of MI. The study protocol was approved by the Institutional Review Board (Helsinki Committee), and written informed consent was obtained from all participants.

All patients recruited into the main study in 16 centers in our region were asked to volunteer for the ACTION calcification side arm study. Over the course of 16 months between June 1997 and October 1998, 518 patients were enrolled. All patients were referred to a single center for a baseline CT to measure coronary, valvular, and thoracic aortic calcification and repeated the test every 2 years thereafter for the next 6 years. The primary CT scans are the basis of this study. After the exclusion of patients because of technical reasons (suboptimal images, pacemakers, and coronary artery bypass grafting staple interference on CT) and a loss to follow-up of 71 patients, a total of 361 patients were included in this study (307 men, 54 women; age range, 37 to 83 years).

Spiral CT: Image Acquisition

CT scan was performed according to a previously described protocol with a commercially available double-helical scanner (Twin, Philips Ltd, Cleveland, Ohio) and spiral scanning mode (without injection of contrast material). Scanning time was 1 second for 2 continuous 2.5-mm sections and 15 to 22 seconds for the entire zone of interest. Examination was performed during a single, unforced, withheld inspiration. During helical scanning, with the tube rotating at 1 revolution per second and the table moving at 5 mm/s with a 1:1 scanning pitch, images were obtained with an effective section thickness of 3.2 mm (a nominal section width of 2.5 mm) and a reconstruction increment of 1.5 mm (overlapping section method). Scanning was performed with 120 kV (peak) and 210 mA, standard resolution, and a 43-cm field of view. For scoring of calcification, the 40 most cephalic contiguous sections were selected, starting at the level of the first visible coronary artery (left main coronary artery or left anterior descending artery). This provided 6-cm coverage of the proximal portion of the coronary tree, including the ascending aorta, and proximal 10 cm of the descending aorta without the aortic arch.

Determination of Calcification

Positive test for the presence of calcification of the aorta was defined as the presence of at least 1 detectable lesion of calcified deposit within the area of the aorta wall. The severity of the calcification was assessed by the number of consecutive slices in which calcium was present and by the area and volume of calcification.

Aortic Calcification and Cardiovascular Events

Table 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>With Aortic Calcification (n = 253)</th>
<th>Without Aortic Calcification (n = 108)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>65 ± 7</td>
<td>55 ± 9</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>213/40</td>
<td>94/14</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>132 (52)</td>
<td>60 (55)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>67 (26)</td>
<td>30 (27)</td>
</tr>
<tr>
<td>Family history of CHD, n (%)</td>
<td>97 (38)</td>
<td>47 (43)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>154 (76)</td>
<td>77 (75)</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>32 (13)</td>
<td>28 (26)</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
<td>27 ± 4</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>100 (39)</td>
<td>32 (31)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>190 (75)</td>
<td>81 (75)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>185 (73)</td>
<td>73 (68)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>187 (74)</td>
<td>80 (74)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>88 (35)</td>
<td>27 (25)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>20 (8)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>CHD history, n (%)</td>
<td>212 (84)</td>
<td>95 (88)</td>
</tr>
<tr>
<td>MI history, n (%)</td>
<td>122 (48)</td>
<td>56 (51)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; BMI, body mass index; and ACE, angiotensin-converting enzyme.

Aortic valve calcification and mitral valve calcification were defined by CT as any visually detected calcified deposit in the region of the aortic valve and mitral annulus, respectively. A coronary calcified lesion was defined as an area within a coronary artery with CT attenuation above a threshold of 90 Hounsfield units (HU) and covering an area of at least 0.5 mm². Regions of interest around all calcification sites were placed by an experienced reader and were automatically analyzed by the Philips software. A modification of Agatston’s scoring method was applied with a threshold of 90 HU instead of 130 HU, and an attenuation factor for each lesion was determined: 1 = 90 to 199 HU, 2 = 200 to 299 HU, 3 = 300 to 399 HU, and 4 = 400+ HU. Coronary calcium score for each region of interest was calculated automatically by multiplying the attenuation factor by the area.

Risk Factors

All patients had stable angina pectoris. The following cardiovascular risk factors were evaluated: hypertension, diabetes mellitus, hypercholesterolemia, smoking, and positive family history of coronary heart disease. Hypertension was defined as blood pressure ≥140/90 mm Hg; diabetes mellitus was defined as hyperglycemia requiring previous or ongoing pharmacological therapy; hypercholesterolemia was defined as a total cholesterol level of >200 mg/dL; and smoking was defined as >10 pack-years of cigarette use in addition to current smoking.

During a period of 4.5 to 6 years of follow-up, we recorded first cardiovascular events that occurred from the beginning of the study comprising cardiac cause of death, acute MI, refractory angina, and stroke. Noncardiac cause of death, heart failure, and peripheral revascularization also were recorded. All events have been confirmed by the independent ACTION events committee.

Statistical Analysis

Data were analyzed with SPSS software version 14.0 (SPSS Inc, Chicago, Ill). Associations of aortic calcification and baseline characteristics, risk factors, and coronary calcification were assessed.
by the independent \( t \) test for continuous variables and by the \( \chi^2 \) test for categorical variables.

Two outcome measurements were assessed: cardiovascular events (cardiac cause of death, acute MI, refractory angina, and stroke) and death. The relationships between these outcomes and aortic calcification were analyzed by Fisher’s exact test for categorical variables and an independent \( t \) test for continuous variables. Survival times to event were calculated as the time from baseline to event or the time from baseline to end of follow-up. Age-adjusted hazard ratios (HRs) for all outcomes were performed with Cox proportional-regression models. HRs and 95% CIs of aortic calcification were calculated from the Cox models to estimate the risk of each outcome. Kaplan–Meier curves of time to total events and cardiovascular events were plotted in accordance with aortic calcification. Patients also were categorized into 4 independent subgroups by aortic calcification: patients with both ascending and descending aortic calcification, patients with only ascending calcification, patients with only descending calcification, and patients with neither. The relationships between the 4 subgroups and outcome events were analyzed by the \( \chi^2 \) test. The differences between the 4 subgroups and the severity of calcification, as measured by slices, area, and volume, were analyzed by ANOVA.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

A total of 361 patients with stable angina pectoris were included in the study. The aortic calcification group included 253 patients (70% of all patients; 213 men, 40 women; mean age, 65±7 years; age range, 41 to 83 years). The comparison group (non–aortic calcification group) included 108 patients (94 men, 14 women; mean age, 55±9 years; age range, 37 to 77 years). Patients with aortic calcification were older (\( P<0.001 \)) and fewer were classified as smokers (13% versus 26%; \( P=0.014 \)) compared with their counterparts without aortic calcification. Medications of patients with compared with those without aortic calcification included more calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics (\( P=0.047, P=0.043, \) and \( P=0.018 \), respectively). There were no additional statistically significant intergroup differences regarding risk factors for atherosclerosis (Table 1). Significant differences were found between patients with and without aortic calcification for the presence of aortic valve calcification (28% versus 11%; \( P<0.001 \)), mitral annulus calcification (29% versus 4%; \( P<0.001 \)), and coronary calcification as expressed by coronary calcium score (\( P<0.001 \)) (Table 2).

During 4.5 to 6 years of follow-up, a total of 89 events were recorded: 75 events in those with aortic calcification compared with 14 events in those without (29% of patients versus 14% of patients, respectively; \( P=0.001 \)). Sixty had cardiovascular events (18.9% of patients with aortic calcifications versus 11.1% in those without; \( P=0.043 \)), which included cardiac cause of death, acute MI, refractory angina, and stroke (8 versus 0 events, 21 versus 5 events, 12 versus 5 events, and 7 versus 2 events, respectively). Total events also included noncardiac cause of death, heart failure, and peripheral revascularization (9 versus 0 events, 7 versus 0 events, and 11 versus 2 events, respectively). A total of 19 patients died during follow-up, all of whom were in the aortic calcification group: 8 deaths were attributed to cardiac cause, 9 were determined to be noncardiac cause, and 2 were of unknown cause. Table 3 summarizes the incidence of events among the patients. Age-adjusted HRs for total events and cardiovascular events by aortic calcification were 2.84 (95% CI, 1.52 to 5.30; \( P=0.001 \)) and 2.70 (95% CI, 1.33 to 5.47; \( P=0.006 \)), respectively. We performed a multivariable analysis adjusted for age, sex, body mass index, hypertension, smoking, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, and coronary artery bypass graft history. HRs for total events and cardiovascular events in patients with aortic calcification were 2.79 (95% CI, 1.46 to 5.20; \( P=0.002 \)) and 4.65 (95% CI, 1.19 to 18.26; \( P=0.028 \)), respectively. Kaplan–Meier curves of time to total events and cardiovascular events in accordance with aortic calcification are presented in Figure 1.

To assess whether the association between aortic calcification and rate of cardiovascular and total events persisted in diverse categories, rate of events was determined in patients according to current smoking, sex, age, history of MI, and coronary artery bypass graft (Table 4). A higher incidence of cardiovascular events and total events was found in aortic calcification subgroups regardless of these characteristics, except for cardiovascular events in woman.

To assess the difference between ascending aorta and descending aorta, we divided the patients into 4 subgroups: those without calcification (\( n=108 \)), those with ascending aortic calcification only (\( n=41 \)), those with descending aortic calcification only (\( n=79 \)), and those with both ascending and

### Table 2. Rate of Calcifications in Study Cohort

<table>
<thead>
<tr>
<th>Calcification Type</th>
<th>With Aortic Calcification</th>
<th>Without Aortic Calcification</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve calcification, n (%)</td>
<td>72 (28)</td>
<td>12 (11)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Mitral annulus calcification, n (%)</td>
<td>73 (29)</td>
<td>4 (4)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Coronary calcium score (mean±SD)</td>
<td>565±735</td>
<td>241±339</td>
<td>(&lt;0.001)</td>
</tr>
</tbody>
</table>

### Table 3. Incidence of Events in Study Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Total events*</th>
<th>All cardiovascular events†</th>
<th>( P )</th>
<th>Age-Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Aortic Calcification (( n=253 )), n (%)</td>
<td>75 (29)</td>
<td>48 (18.9)</td>
<td>0.001</td>
<td>2.84 (1.52–5.30)</td>
</tr>
<tr>
<td>Without Aortic Calcification (( n=108 )), n (%)</td>
<td>14 (13)</td>
<td>12 (11.1)</td>
<td>0.006</td>
<td>2.70 (1.33–5.47)</td>
</tr>
</tbody>
</table>

*Total events included cardiovascular events, noncardiac cause of death, heart failure, and peripheral revascularization.
†All cardiovascular events included cardiac cause of death, acute MI, refractory angina, and stroke.
descending aortic calcification (n=133). Mean age was significantly different between the 4 groups (55±9, 62.6±7, 63.7±9, and 66.3±7 years, respectively; *P*<0.001). The proportion of patients >65 years of age in the 4 subgroups was 27.8%, 46.3%, 54.5%, and 68.2%, respectively (*P*<0.001). There were no additional intergroup significant characteristic differences. Age-adjusted rate of all events, cardiovascular events, acute MI, and death in the descending aortic calcification subgroup was considerably higher compared with all other subgroups (*P*<0.001, *P*=0.013, *P*=0.003, and *P*=0.002, respectively).
Table 4. Incidence Rate of Cardiovascular Events and Total Events Among Study Patients According to the Following Characteristics: Smoking, Sex, Age, History of MI, and CABG

<table>
<thead>
<tr>
<th>Cardiovascular Events</th>
<th>Total Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Aortic Calcification</td>
</tr>
<tr>
<td></td>
<td>Without Aortic Calcification</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (11)</td>
</tr>
<tr>
<td>No</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
</tr>
<tr>
<td>&gt;60 y</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>70 ± 6</td>
</tr>
<tr>
<td>&lt;60 y</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48 ± 6</td>
</tr>
<tr>
<td>MI history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (13)</td>
</tr>
<tr>
<td>No</td>
<td>6 (11)</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (20)</td>
</tr>
<tr>
<td>No</td>
<td>9 (10)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft.

Discussion

Spiral CT is a rapidly evolving and effective noninvasive technique for cardiac imaging that is increasingly being used. This technique has improved greatly since the development of multirow detector CT scanners with faster acquisition speed. In recent years, there has been great ongoing interest regarding vascular calcification and its association with clinical outcomes. It is well known that calcification is related to atherosclerosis, yet whether it has a direct detrimental effect or is simply a marker of atherosclerotic burden is unknown. Studies in coronary arteries demonstrate an association between calcification and cardiovascular events, in particular MI. The relation between atherosclerosis and calcification of the thoracic aorta is complex. As opposed to the atherosclerotic nature of coronary calcification, aortic calcification can be divided into 2 pathophysiological processes: intimal, which is mostly atherosclerotic, and medial, which is not atherosclerotic. Currently, helical CT cannot differentiate accurately between intimal and medial calcifications, yet it is a highly sensitive method for detecting vascular calcium. In recent years, few studies have shown the association between coronary, valvular, and aortic calcification.

The hypothesis that aortic calcification has an underlying atherosclerosis process also was established in several trials demonstrating an increased risk of cardiovascular and cerebrovascular events in patients with aortic calcification in several imaging techniques. We assessed the hypothesis that aortic calcification has important clinical implications on outcome and events in stable angina pectoris patients. We found that aortic calcification, as measured by CT, is significantly associated with death and cardiovascular events. We have demonstrated that descending aortic calcification, in particular, is more dominant in all events compared with ascending aortic calcification and both ascending and descending calcification. This is overpowered by the fact that the severity of calcification in the descending aorta was higher compared with the other subgroups. Therefore, calcification of the descending aorta may be a better marker of increased burden of vascular disease than ascending aortic calcification. This finding has no apparent cause and is worthy of future investigation. Another finding that remains to be determined is whether aortic calcification is related to all-cause mortality. In recent years, there have been several reports regarding the association of all-cause mortality and calcification. Budoff et al investigated >25,000 patients in an observational outcomes study and found that coronary artery calcium provides incremental information in addition to traditional risk factors in the prediction of all-cause mortality. This association also was demonstrated in elderly male patients. Few studies have tried to assess whether aortic calcification is associated with all-cause mortality. Abdominal aortic calcification was associated with all-cause mortality in hemodialysis patients and in elderly women. Furthermore, aortic annular calcification was associated with cardiovascular and all-cause mortality in older patients with preexisting cardiovascular disease as demonstrated by echocardiography. No study has investigated the association between thoracic aortic calcification and all-cause mortality in patients with stable angina pectoris or by CT, and our study, although with a small number of deaths, demonstrates this association. The cause of the association between calcification and all-cause mortality remains to be determined, but our results strengthen the hypothesis that aortic calcification is simply associated with atherosclerosis, yet it remains unclear which additional contributing factors affect this process.

Study Limitations

The limitations of our study include several issues regarding patient characteristics. First, in our unique cohort of patients, those with aortic calcification were significantly older than their counterparts without aortic calcification. Thus, we have performed age adjustment and multivariable analysis and investigated the incidence of events in several subgroups of patients according to their age. Second, as shown in Table 1, intergroup differences also included cigarette smoking and use of several medications (calcium channel blockers, angio-
tensin-converting enzyme inhibitors, and diuretics). All these characteristics, including history of coronary artery bypass graft, were included in the multivariable analysis. Third, smokers in our study were those who smoked >10 pack-years in addition to current smoking. We have not recorded any data regarding past smokers with no current smoking. Our study cohort also was limited to patients with stable angina pectoris and therefore may not be generalized to other populations. As a consequence of the unique study cohort, a significant proportion of the study population had a cardiovascular event in the past. This is one of the outcomes measured; therefore, in our study, we have recorded only the first events. Because of the relatively small number of cardiovascular events, the CI for the HR for cardiovascular events was wide (95% CI, 1.19 to 18.26). Sex also was a confounder in our cohort. Only 54 women were included in our study, in whom 9 events occurred. Therefore, we have not looked at subgroups based on sex. Another limitation is the fact that noncalcified atherosclerotic plaques could not be diagnosed by spiral CT and that the aortic arch was not assessed. In addition, newer and faster multislice spiral CT modalities have been developed and have high sensitivity in assessing the presence and extent of calcium deposits in the aorta.

Conclusions
The present study demonstrates that calcification of the thoracic aorta is highly prevalent in stable angina pectoris patients. It is age related and associated with coronary calcification and valvular calcification. Thoracic aortic calcification, particularly descending aortic calcification, is associated with an increased rate of death and cardiovascular disease.

Disclosures
None.

References
Calcification of the thoracic aorta is associated with atherosclerotic risk factors. It is a common finding as an incidental finding in chest x-ray or in more advanced imaging techniques. Because only a few studies have investigated its clinical implications, this finding is usually overlooked and regarded as clinically insignificant. To assess the clinical importance of thoracic aortic calcification and by that raise the question of whether the practicing clinician should modify the approach to the patient with aortic calcification by screening modalities, risk factor stratification, or treatment. This question has yet to be answered, and further evidence-based investigation is needed to determine the clinical outcome and management of the patient with thoracic aortic calcification.
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