Coronary artery calcification is reappearing as the subject of clinical investigation. In the late 1960s, fluoroscopic examination for coronary artery calcification began with the recognition that visible calcific deposits implied atherosclerosis in the coronary artery wall. The calcification could be detected rapidly and noninvasively (1). Despite many studies, the clinical relevance of a positive test was unclear. Apparent discrepancies between the degree of calcification and angiographic disease severity led to skepticism about its clinical usefulness. Coronary fluoroscopy subsequently fell into disuse as treadmill exercise testing and nuclear cardiac imaging became available. Although coronary fluoroscopy furnished anatomic information about the disease status of the arterial wall, the exercise tests detected lumen obstruction and physiologic effects of obstructive disease. The clinical utility of detecting coronary calcification was never directly established, and to this date it remains unresolved despite many publications on the subject (2–4).

The present study. In this issue of the Journal, Detrano et al. (5) report a prospective study of 1,461 asymptomatic patients (1,281 men and 180 women; with a mean age of 63 years). This cohort was recruited on a referral basis from patients answering public advertisements to participate in coronary screening. The resulting sample was a high risk group, evidenced by their risk factor profile: 21% were smokers; 52% were hypertensive by history; 44% had first-degree relatives with coronary artery disease; and the mean (±SD) total and high density lipoprotein (HDL) cholesterol levels were 241 ± 49 and 44 ± 14 mg/dl, respectively. Cinefluoroscopy was performed in all patients to detect coronary artery calcification. Follow-up at 1 year showed interesting results: fluoroscopy positive for coronary artery calcification indicated a risk ratio of 2.7 for the combined end points of angina pectoris, death from coronary heart disease, nonfatal myocardial infarction or myocardial revascularization. Coronary events occurred in 37 of 691 patients with fluoroscopic calcification, whereas 15 of 768 patients negative for calcification had similar events. The detection of coronary artery calcium independently predicted at least one coronary event end point, controlling for age, gender and all other risk factors. Three patients with calcification died of cardiac causes. However, fluoroscopic calcium was not associated with coronary death or silent myocardial infarction when considered as a separate end point because three cardiac deaths and one nonfatal myocardial infarction occurred in the patients without detectable calcium.

The importance of this study is that a simple, noninvasive examination enhanced prognostic information for myocardial events beyond the usual clinical risk factors. These results are consistent with previous observations about coronary artery calcium and prognosis in patients with known coronary artery disease (6,7). Margolis et al. (7) reported that fluoroscopic coronary artery calcification provided potent prognostic power in patients undergoing coronary angiography. In this study, a 5-year patient survival rate of 58% was found in patients with calcification compared with 87% in those without calcification. Other studies have shown that calcification is a good method of noninvasively detecting asymptomatic angiographic coronary artery disease. In a cohort of young, asymptomatic U.S. Air Force aviators, Loecker et al. (8) found that fluoroscopic calcification was associated with a sensitivity and specificity of 61% and 86% for angiographic coronary artery disease, respectively. Although most of the detectable disease in this study was angiographically "mild" (<50% diameter stenosis), the test performed as well as exercise treadmill testing and planar thallium scintigraphy.

The present study is the most recent to show rekindled interest in detecting coronary artery calcification as a noninvasive marker for coronary atherosclerosis (9,10). Calcium deposition in the coronary arteries virtually always indicates atherosclerosis because nonatheromatous coronary artery calcification occurs very rarely, typically in Mönckeberg's sclerosis and Kawasaki disease (11,12). Asymptomatic and, frequently, nonobstructive coronary atherosclerosis may thus be diagnosed by detecting calcification because atherosclerotic plaque typically enlarges the coronary artery before lumen stenosis occurs (13,14). The obvious question concerns the clinical value of detecting asymptomatic coronary atherosclerosis.

Coronary calcium and detection of coronary artery disease. Coronary atherosclerosis is the most common cause of death in adult Americans today. The annual coronary event rate in the asymptomatic general population ≥40 years old is ~1% (15). The ability to detect coronary artery disease in its subclinical state has intuitive appeal because nonobstructive lesions are a known cause of catastrophic clinical events, including sudden death, myocardial infarction and unstable angina (16–18). Although the clinical value of disease detec-
tion in a subclinical state seems obvious, it is unproven and remains clouded by a number of issues.

In the asymptomatic general population the proportion of subjects having coronary artery calcification may far exceed the number who will have a clinical coronary event during their lifetime. The likelihood that asymptomatic coronary atherosclerosis will cause morbidity or mortality is unknown but could be quite low, as suggested by a high disease prevalence yet low event incidence. Can subclinical coronary atherosclerosis thus be considered a "benign" condition if clinical manifestations occur in only a small fraction of diseased patients? The major problem with diagnosing subclinical coronary disease is thus highlighted: Few affected patients may suffer clinical problems from this condition. The significance of subclinical disease detection is clearly tempered by the observation that it is not presently possible to determine which patient will develop clinical illness, catastrophic as it may be. The "false positive" rate from detecting calcification may be unacceptably high owing to few clinical events in many patients testing positive for coronary calcification.

Clinical relevance of coronary calcium. What clinically relevant information can be inferred from noninvasive calcium detection? The Detrano et al. (5) study suggests the most likely use—to augment traditional risk stratification for coronary events in asymptomatic patients. Other possibilities must be studied further:

1. Do other aspects of calcification determination exist (such as anatomic location, density or calcific volume) that might distinguish patients who will have events from those who will not? Can the type of event be predicted? When asymptomatic patients with coronary atherosclerosis become symptomatic, their first presentation is angina pectoris in ~70% of cases (19). Can calcification detection predict more dangerous events? The Detrano et al. (5) study suggests that this may not be the case, finding a risk ratio of 1.0 for cardiac death. This was countered, however, by a risk ratio of 10.0 (p = 0.02) for nonfatal myocardial infarction in patients with calcification. Clearly, longer term follow-up and larger numbers will clarify this issue.

2. Might quantitation of coronary calcification by technologies such as electron beam computed tomography (20) estimate disease severity? At present, electron beam computed tomography appears to be only moderately useful in this application (21-23). Although it is true that a relation exists between the volume of calcification in a plaque and the corresponding lumen stenosis, there is great variability in stenosis severity for both large and small calcific volumes (24,25). Histologically proved total occlusions have been found with no associated calcification. Conversely, small plaques are sometimes heavily calcified.

3. Does calcification detection augment prognostication already available by stress testing with or without nuclear imaging in selected patient groups? Calcification detects anatomic disease, whereas stress testing detects the physiologic consequences of flow-limiting lesions. Much has been written about prognostic information from stress testing (26,27). Does synergy exist between these methodologies, or is prognostic information from calcium detection redundant?

4. Do small calcific deposits represent "early" coronary atherosclerosis that will progress? Is progression inevitable in all patients? Can calcification studies determine which younger patients will progress over the long term to severe, clinical coronary artery disease? Longitudinal studies will be necessary to answer these questions.

5. Can the effects of risk factor modification be followed up noninvasively by calcium determination (28)? Atherosclerosis regression trials suggest that aggressive risk factor management can reduce angiographic stenosis. These angiographic end points are costly to obtain and expose patients to small but finite risks. The availability of a noninvasive measure of treatment efficacy would be of substantial clinical benefit in following up therapeutic efficacy.

Because determination of angiographic disease severity by calcification appears limited, prognostication and identification of clinical risk may be the "make-or-break" hurdle for this test. Promise in this regard is suggested by the results of the Detrano et al. (5) study but will require extension to longer times and additional patient groups. Meanwhile, restraint should be exercised in avoiding "screening" asymptomatic patients for coronary calcification until more knowledge is gained about how to interpret and act on test results. The work of Detrano et al. suggests that additional studies are indeed worthy of pursuit.

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References


