Coronary Artery Calcium
Should We Rely on This Surrogate Marker?
Rita F. Redberg, MD, MSc

Surrogate markers of atherosclerosis such as treadmill time, serum tests, coronary artery calcium, and carotid intimal thickness enjoy considerable attention and the promise of yielding answers at much less cost and time than clinical trials using hard clinical outcomes such as myocardial infarction and cardiac death. Indeed, only studies with large sample sizes and long follow-up periods can provide meaningful data on hard outcomes. Of course, from a patient care perspective, the value of a surrogate marker derives solely from its ability to predict a cardiac event giving rise to either death or physical impairment that could be prevented. What is important to patients is whether a new therapy can make one feel better or live longer (or both). Few patients would eagerly undergo a new treatment if it would merely change a measurement but would not also improve how they felt, would not reduce their risk of heart attacks, and/or would not help them to live longer.

Article p 427

Cardiologists’ recent experience with hormone replacement therapy (HRT) once again illustrated the dangers of relying too heavily on surrogate markers. Multiple studies of HRT using surrogate markers showed a benefit on cardiovascular disease. The Postmenopausal Estrogen/Progestin Intervention (PEPI) trial, for example, showed that HRT had beneficial effect on serum markers of atherosclerosis, with lower low-density lipoprotein (LDL) and fibrinogen levels and higher high-density lipoprotein. The Rancho Bernado Study found that women taking HRT had lower coronary artery calcium (CAC) scores and concluded that there was antiatherogenic effect of postmenopausal estrogen (but nevertheless called for a clinical trial to exclude confounding by social class, lifestyle, and unmeasured covariates). Despite the plethora of studies suggesting beneficial effects of HRT on surrogate markers of atherosclerosis, subsequent randomized clinical trials using hard clinical outcomes revealed that HRT does not prevent cardiovascular disease; indeed, some data raised questions of harm. One important lesson from this experience is that surrogate markers of atherosclerosis may not be reliable predictors of clinical events.

In this issue of Circulation, Schermund et al present the results of a multicenter German randomized controlled trial of intensive (80 mg) atorvastatin versus standard (10 mg) atorvastatin for atherosclerosis, with CAC volume scores as the primary end point. They randomized a total of 471 persons, all of whom received 4 weeks of 10 mg atorvastatin and a baseline calcium scan before entering the study. After 1 year of lipid-lowering therapy, the coronary calcium scan was repeated. As expected, there was more LDL lowering (20% greater) in the intensive treatment group. However, the investigators found no difference in atherosclerosis progression, as measured by CAC volume scores, between intensive and standard lipid-lowering therapy; CAC scores in both groups increased by ≈26%. Surprisingly, atherosclerosis as measured by CAC progression showed no relationship to LDL cholesterol levels. Because LDL cholesterol has been shown to be clearly related to cardiac events, the lack of relationship of LDL levels to CAC is perplexing and raises questions about the association of CAC with cardiac events.

Several randomized control trials such as Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT), Treating to New Targets (TNT), A to Z, and Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) have found a benefit with intensive statin therapy using clinical end points. The reason for the apparently contradictory findings in the present study is unclear, but possible explanations include the following: (1) There is no difference in efficacy on atherosclerosis progression between intensive versus standard dose atorvastatin; (2) the follow-up period was not long enough to see a difference in calcium scores; (3) intensive lipid lowering is of benefit only for secondary prevention; and/or (4) CAC volume scores are not especially reliable markers of cardiac events.

With regard to the first point, the authors did find the expected decreases in LDL with statin therapy, with greater effect in the intensive-dose group than in the standard-dose group. These results are comparable to the decrease in LDL seen in trials showing reductions in cardiac events in intensively treated groups. Thus, one would expect similar outcomes in this trial, casting doubt on a difference in efficacy of higher-dose statins to explain the disparity in results.

Regarding the follow-up period, previous trials of intensive versus standard statin regimens have shown that a reduction in risk of death and major cardiovascular events emerges rapidly. One smaller (n = 299) nonrandomized study found that statin therapy induced a 61% reduction in the rate of coronary calcium progression after 1 year, leading its authors...
to conclude that electron-beam computed tomography is a useful tool over relatively short time periods.\(^9\)

As for the third point, all of the previous intensive versus standard statin treatment trials have been in patients with known coronary artery disease; it is possible that this group of patients with risk factors but no known coronary artery disease did not have enough baseline risk to benefit from a more aggressive primary prevention strategy.

Finally, the last possible explanation—that CAC scores may not reliably predict cardiac events—legitimately bears further scrutiny. Multiple studies have shown that intensive lipid lowering is associated with fewer cardiac events than standard lipid lowering.\(^10\)

Could the failure of the new German study to find lower CAC scores in the intensively treated statin group be explained by its use of surrogate end points, which may not be reliable substitutes for cardiac events? Surrogate markers such as CAC or carotid intima-media thickness are certainly associated with atherosclerosis. However, atherosclerosis is widespread, often referred to as the scourge of Western Society, and does not always lead to clinical cardiac events. In fact, it is often present in the absence of clinical disease. The number of people with CAC is 10 to 100 times greater than the number of persons that will ever get heart disease.\(^11\)

Thus, it is not surprising that markers of atherosclerosis such as CAC do not follow the pattern we would expect to see for cardiac events. Indeed, in 1988, Ambrose et al\(^12\) showed that even coronary angiography could not predict future myocardial infarction because myocardial infarction frequently develops from previously nonsevere lesions.\(^12\) CAC is associated with atherosclerosis, but atherosclerosis cannot reliably predict events in an individual (even though it is associated with cardiac events at a population level). Furthermore, although there is clearly a relationship between CAC and subsequent cardiac events, whether there exists a meaningful incremental value of CAC over prediction by risk factor assessment such as the Framingham Risk Score (FRS) remains unproven. One South Bay Heart Watch publication reported an incremental value of CAC over FRS for risk prediction; the area under the receiver-operator characteristic curve went from 0.63 for FRS to 0.68 for FRS plus CAC.\(^13\)

The key question remains: Even if CAC is a predictor of cardiac events, is it a better predictor than FRS alone?

Several other recent studies such as the Beyond Endorsed Lipid Lowering With EBT Scanning (BELLES) study\(^14\) and the St Francis Heart Study\(^15\) that similarly use CAC scores to measure outcomes of various statin regimens also found that statin therapy did not affect atherosclerosis progression as measured by CAC scores. The current German study, like several before it, again cautions against being misled by undue reliance on surrogate markers. Shorter, less expensive studies using surrogate markers may provide practical and valuable information, but only if these markers are reliable surrogates for clinically meaningful events. The jury is still out, but as of now, the weight of the evidence suggests that CAC scores are not reliable predictors of cardiac events.

Disclosures

None.

References


Key Words: Editorials • calcium • imaging • lipids
Coronary Artery Calcium: Should We Rely on This Surrogate Marker?
Rita F. Redberg

Circulation. 2006;113:336-337
doi: 10.1161/CIRCULATIONAHA.105.600676
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/113/3/336

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 Circulation is online at:
http://circ.ahajournals.org//subscriptions/