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Visualizing coronary calcium is associated with improvements in adherence to statin therapy

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Abstract

Background: Many patients lack motivation to control cardiovascular risk factors and clinicians have long sought ways to activate apathetic patients. Despite significant and consistent data on the benefits of lipid-lowering agents to reduce cardiovascular events, adherence and utilization of these agents remains low. We evaluated whether visualization of coronary calcium would positively affect patients' adherence rates.

Methods: We evaluated patients who underwent electron beam tomography (EBT) coronary calcium evaluation at least 1 year prior with a survey questioning them about health behaviors. Patients filled out baseline and follow-up questionnaires relating to lifestyle modifications, including statin utilization, diet, exercise, tobacco cessation and vitamin/antioxidant utilization.

Results: The study population consisted of 505 individuals on statin therapy on baseline who were followed for a mean of 3 ± 2 years. Overall the statin compliance was lowest (44%) among those with CAC score in the first quartile (0–30), whereas 91% of individuals with baseline CAC score in the fourth quartile ($\geq$526) adhered to statin therapy. In multivariable analysis, after adjusting for cardiovascular risk factors, age, and gender, higher baseline CAC scores were strongly associated with adherence to statin therapy.

Conclusions: In addition to risk stratification for the asymptomatic person, patients visualizing coronary artery calcium may improve utilization and adherence to lipid-lowering therapy. Outcome studies and randomized trials need to be done to quantify the true value and cost-effectiveness of this approach.

Keywords: Computed tomography; Electron beam; Adherence; Coronary artery calcification; Statin therapy

Despite convincing data demonstrating the benefits of lipid lowering agents for both primary and secondary prevention of coronary events [1–3] these agents remain underused by high-risk patients and health-care providers [4]. Furthermore, long-term adherence to these therapies remains poor among primary prevention cohorts [5] and even among patients who survive myocardial infarction [6]. Thus, effective interventions that improve their use and/or adherence are urgently needed [7].

We evaluated the association between electron beam tomography (EBT) coronary calcium measurement and adherence to lipid lowering therapy and lifestyle modifications among consecutive patients physician-referred to our center for evaluation of coronary atherosclerosis. We hypothesized that patient knowledge of increasing coronary artery calcium (CAC) burden would be associated with improved patient adherence to coronary risk reducing behaviors, such

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as lipid lowering therapy, exercise, diet and smoking cessation.

1. Methods

A total of 1215 consecutive asymptomatic patients referred for EBT risk assessment by their primary physician were sent a survey questioning them about health behaviors. Demographic characteristics, lifestyle behaviors including cigarette smoking, alcohol use, physical activity, diet, physician diagnosed diseases, current medications including statin utilization, vitamin/antioxidant utilization, hospitalizations and surgeries were determined using structured questionnaires. The presence and number of risk factors for a participant was calculated based on the National Cholesterol Education Program guidelines [8]. Risk factors included: males age >45 years, females >age 55 years, current cigarette smoking, history of premature coronary disease in first-degree relative, hypertension and hypercholesterolemia. Current cigarette smoking was defined as use of >10 cigarettes per day. Hypertension was defined by current use of anti-hypertensive medication or known and untreated hypertension. Hypercholesterolemia was defined as use of cholesterol lowering medication or, in the absence of cholesterol lowering medication use, as having a total serum cholesterol >240 mg/dL. Patients underwent coronary calcium scanning using the Electron Beam Tomography C150XL (GE, South San Francisco, CA), using 3 mm slices and Agatston scoring, as previously described [9]. Patients were also shown the actual scan, seeing the coronary calcium as bright white spots in their coronary arteries, describing the atherosclerosis visualized as: none, mild, moderate or severe. At the time of the original scan, we discussed scan results with patients, describing CAC as identifying underlying coronary atherosclerosis and being predictive of heart disease risk. Patients filled out a questionnaire related to risk factors, lifestyle and medication usage at baseline (time of calcium scan). The same survey was given again at follow-up, to evaluate changes in behavior or medication over the interval. A sample question from the questionnaire was “Are you currently taking a statin cholesterol-lowering agent? if so, which one”. This allowed us to assess whether those who were on statin therapy at baseline were still on statin therapy at follow-up.

Patients with baseline known cardiovascular disease (including stroke, claudication or coronary artery disease) were not included in the study. Patients experiencing an interim cardiac event (revascularization, stroke, myocardial infarction, new onset chest pain) were excluded ($n = 105$). Follow-up survey information was obtained in 981 of 1110 (88%) of patients, a mean of 3.6 ± 2 years after the baseline scan. There were no differences in the prevalence of risk factors and CAC characteristics between responders and non-responders. Since the main aim of the study was to assess compliance on statin therapy, 476/981 individuals who were not on statin therapy were excluded from the final analyses. The study was approved by the Institutional Review Board of our institution.

2. Statistics

Categorical data are presented as number (percent), and continuous data as mean value $\pm$ S.D. Two tailed Chi-squared test and the *t*-test or Mann–Whitney rank sum test were used for analysis of categorical and continuous variables, respectively. ANOVA was used for univariate analysis of categorical variables and adherence to statin therapy across CAC quartiles. Hypertension, hypercholesterolemia, tobacco use, diabetes, age, gender, family history of premature heart disease, as well changes in behavior, such as increased physical activity, utilization of aspirin and change of diet, were variables included in the multivariable analysis using logistic regression. Risk-adjusted (i.e., controlling for cardiac risk factors) odds ratio for adherence with statins with increasing CAC quartiles were compared with lowest quartiles as well additionally with CAC scores of 1–99.9, 100–399.9 and $\geq$400 with no CAC, respectively. Higher levels of baseline risk factors are associated with increased calcification. Therefore, to control for a possible treatment bias due to higher levels of baseline cardiovascular risk factors, we further stratified the population according to presence or absence of CHD risk factors and adjusted for these risk factors in our analysis. Multiple logistic regression models were used to examine the likelihood of statin adherence with increasing baseline CAC scores in a hierarchical fashion:

(I) adjusted for age and gender (model 1);
(II) adjusted for age, gender, hypertension, diabetes, tobacco use and family history (model 2).

All tests of significance were two-tailed, and significance was defined at the 0.05 level or below. Data were analyzed using STATA Version 8 (Austin, TX). No external funding was utilized in this research.

3. Results

The final study population consisted of 505 individuals on statin therapy at baseline. Majority of the study population were men ($n = 413$, 82%). The mean age of the study population was 61 ± 10 years. These patients were followed for 3 ± 2 years (range 1–10 years) Patients were divided into quartiles based upon baseline CAC score (first quartile: 0–30, second quartile: 31–149, third quartile: 151–526 and fourth quartile: $\geq$527). Study participants with higher CAC were more likely to be older, hypertensive, and diabetic (Table 1). The proportion of individuals on statins at baseline increased linearly with increasing CAC quartiles (first quartile: 24%, second quartile: 46%, third quartile: 63% and fourth quartile: 74%, $p < 0.0001$), independent of baseline risk factors.

Table 1
Characteristics of study population at baseline ($n = 505$) according to CAC quartiles

	First quartile (0–30)	Second quartile (31–149)	Third quartile (151–526)	Fourth quartile (≥526)	*p*-Value
Number	128	127	124	126	–
Age (years)	56 ± 9	59 ± 9	62 ± 9	66 ± 8	<0.0001
Hypertension (%)	51	24	34	65	<0.0001
Tobacco use (%)	14	11	12	16	0.7
Diabetes (%)	5	6	9	8	0.6
Family history of premature CHD (%)	69	67	59	70	0.2

Table 2
Lifestyle modifications according to baseline CAC scores

	First quartile (0–30)	Second quartile (31–149)	Third quartile (151–526)	Fourth quartile (≥527)	*p*-Value
Dietary modification	52 (41%)	73 (57%)	74 (61%)	81 (64%)	0.001
Increased cardiovascular exercise	75 (58%)	81 (64%)	85 (70%)	87 (69%)	0.2
Proportion who quit smoking	12/18 (67%)	11/14 (78%)	11/15 (74%)	14/20 (70%)	0.8
Antioxidant use	82 (33%)	87 (36%)	87 (35%)	84 (34%)	0.9

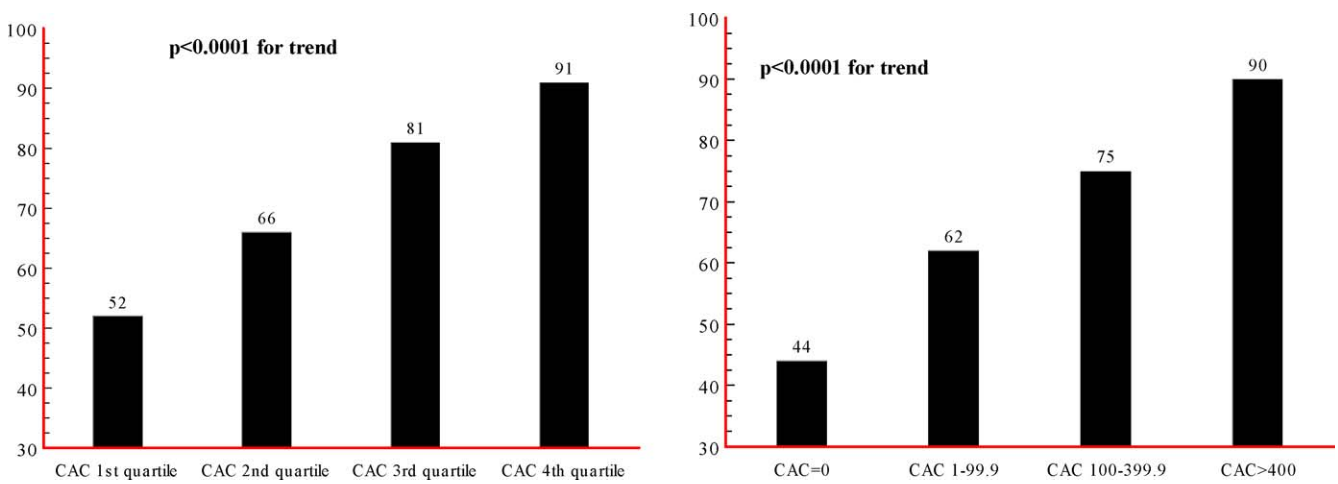

Fig. 1. Percentage (%) of individuals maintaining statin therapy according to baseline CAC.

At follow-up patients in the first score quartile (0–2) were least likely to make any dietary modification or increase cardiovascular exercise (Table 2). Dietary modification (reported as a concerted effort to maintain a healthier diet) increased from 41 to 64% across the four quartiles ($p = 0.001$). Overall a high number of individuals on statin therapy at baseline quit smoking and increased the levels of cardiovascular exercise.

Regarding statin therapy, 366/505 (72%) of statin users at baseline remained on treatment at follow-up. Regarding hypertensive therapy, 196/219 (89%) remained on therapy throughout the observation period. Fig. 1 demonstrates that with increasing CAC score at baseline, the adherence with statins was significantly higher increasing from 52% in quartile 1 to 92% in fourth quartile (scores > 526, $p < 0.001$). A similar trend was also observed with absolute CAC scores; 44% with CAC score of zero adhered to statin therapy at baseline compared to 90% of those with CAC ≥ 400 ($p < 0.0001$ for trend). We then evaluated statin adherence in patients in each calcium score quartile based upon presence or absence of cardiovascular risk factors (Table 3). A similar adherence

Table 3
Proportion (%) of individuals maintaining statin therapy among individuals on statin therapy at baseline according to baseline CHD risk factors

	CAC quartiles				*p*-Value
	First quartile	Second quartile	Third quartile	Fourth quartile	
Hypertension					
Yes	49	70	80	94	<0.0001
No	53	64	81	90	<0.0001
Diabetes					
Yes	33	50	100	80	<0.0001
No	52	67	79	92	<0.0001
Tobacco use					
Yes	51	68	80	91	<0.0001
No	55	50	93	90	<0.0001
FH of premature CHD					
Yes	52	67	78	95	<0.0001
No	46	60	88	83	<0.0001

Table 4
Odds ratio of maintaining statin therapy among individuals on statin therapy at baseline according to baseline CAC quartiles

	First quartile	Second quartile	Third quartile	Fourth quartile
Model 1	1 (Reference)	1.76 (0.93–3.36)	2.94 (1.5–5.65)*	7.99 (3.71–17.19)†
Model 2	1 (Reference)	1.96 (0.97–3.92)	3.27 (1.63–6.53)*	9.26 (4.13–20.76)†

Model 1: adjusted for age and gender; model 2: adjusted for age, gender, hypertension, diabetes, tobacco use and family history.
* $p = 0.001$.
† $p < 0.0001$.

irrespective of presence or absence of CHD risk factors was observed for statin adherence in patients in each calcium score quartiles (Table 4).

In multivariate analyses adjusting for age and gender (model 1), individuals with CAC in the fourth quartile were 9.7 times more likely to adhere to statin therapy compared those to with CAC score in the first quartile (<30). After further adjustment with hypertension, diabetes, tobacco use and family history (model) the results were similar. Patients in the fourth quartile for score were 10.0-(CI 2.3–23.4) fold more likely to persist with lipid lowering therapy. Similarly high likelihood of adherence was observed with scores 1–99, 100–399 and ≥400 compared to those without any CAC (Fig. 2).

4. Discussion

Despite convincing evidence demonstrating substantial morbidity and mortality reductions with the use of statins [1] adherence to lipid lowering agents has been disappointingly low [10]. There is ample evidence that statin therapy is substantially underused, especially in patients at higher risk [11]. Furthermore, the “treatment-risk paradox”, demonstrating that the highest risk patients are often least likely to be treated, represents another important barrier to prevention strategies.

Large trials consistently demonstrate that EBT coronary imaging adds incremental and independent information regarding prognostic risk [12–16] and it is recommended as a potential for risk stratification by both the National Cholesterol Education Panel [17] and Prevention V Guidelines [18]. Patients with advanced subclinical atherosclerosis represent a high-risk subset in primary prevention.

Baseline increasing CAC scores was an independent predictor of maintenance of lipid-lowering use at follow-up. We believe that the improved adherence in our study reflected a change in the patients’ (and their physicians) perceived threat of their atherosclerotic disease was changed after their EBT test, as suggested by many theoretical models of medication adherence [19]. Three quarters (75%) of those on statin therapy and CAC scores of 100–399 at baseline still maintained the therapy at follow-up, whereas the maintenance rate was 90% among those with very high CAC scores (≥400). This pattern, of higher risk patients demonstrating improved adherence, has been widely reported. Large studies demonstrated improved compliance rates of statins among patients with higher severity of cardiac illness [11,20].

Factors that influence compliance include knowledge of the disease, confidence in ability to follow recommended behaviors, as well as perception of health and benefits of therapy or change in behavior [21]. It is possible that seeing the calcification changed their perception of their own health status. This increased motivation and compliance has been reported in previous studies of EBT [24] and is consistent with the explanation given at the time of the scan that high calcium scores are associated with a 10-fold increased

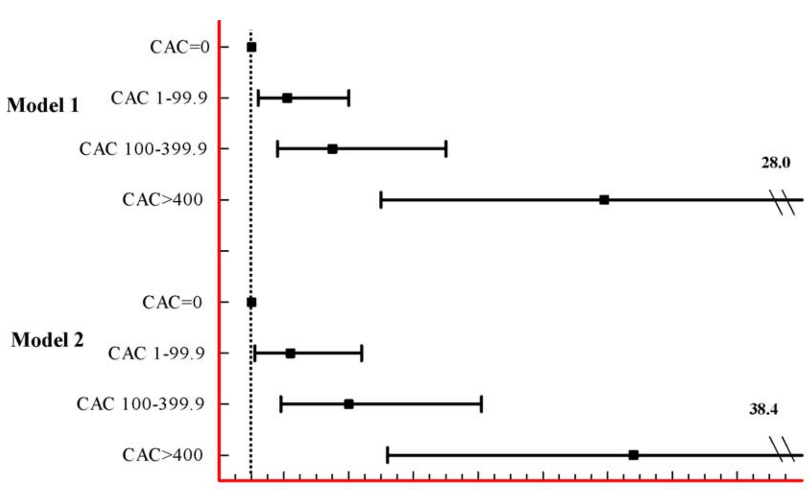

Fig. 2. Odds ratio (95% CI) of maintaining statin therapy with increasing absolute CAC scores (reference group: CAC=0; Model 1: adjusted for age and gender; Model 2: adjusted for age, gender, hypertension, diabetes, tobacco use, and family history).

risk of cardiac events. Such hypothesis for patient behavioral changes are supported by conceptual models of patient adherence that suggest that patient perception of disease threat is an important determinant of patient adherence [22,23]. This is especially important, as atherosclerosis is largely an indolent disease. Furthermore, our patients were physician-referred for EBT assessment, increased and ongoing physician-patient dialogue concerning the patient's CAD risks may have further reinforced the patients' adherence. Data from our center and others [24] suggest that providing patients with EBT findings had significant positive effects on their adherence to cardiac risk reduction behavior.

O'Malley et al. found no association between adherence to lifestyle modification and EBT results [25]. However, there are important limitations to their investigation that may explain differences in results. The population of 450 patients described by O'Malley et al., largely comprised of military personnel (ages 39–45 years) almost exclusively of low risk for coronary artery disease, and were found to have a very low prevalence of CAC (18%). It is unlikely that the 'clean bill of health' (i.e., no or minimal coronary calcification) given to almost all subjects in their study would be a strong motivator of lifestyle change. There were trends toward improvement among persons with abnormal calcium scans, suggesting that intermediate-risk patients may benefit from EBT testing. Examining the subgroup of persons with EBT defined CAC ($n = 59$), the number of adherers (42%) to modification of cardiovascular risk factors was similar to our first or second quartile (46% adherent). Importantly, patients with CAC scores of 0 did not subsequently have behavior associated with higher projected risk, indicating that a score of 0 does not convey false reassurance resulting in adverse behavioral outcomes [25].

There are several limitations to our investigation. First, this study was observational, without a control population. However, the results parallel a randomized control trial, where similar scores yielded similar patient changes [25]. However, since it would be unethical to withhold scan data from patients or their physicians, we must look toward large observational studies for evidence of an association of CAC and adherence. Despite the relative large size of the study, it was not possible to adjust for all potential confounders (influence of physicians, patients underlying motivation, etc.). We carefully corrected and controlled for confounders in the study that might influence compliance. Using multivariable analysis, we controlled for the presence of other risk factors. We also eliminated any patient with an interim cardiovascular event, including the development of symptoms. Second, adherence was measured using a standardized survey. Several investigations have shown that self-reported medicine utilization tends to overestimate adherence [26,27]. However, self-reported adherence does provide important information in variation to clinical response to therapy [28]. The study population is acknowledged to already be a motivated population, as they were physician-referred for CAC scanning. The patients' socioeconomic status and access to health care was uniformly high in this study, so this was most likely not a confounder. The most limiting confounder is that patients with high CAC scores may have subsequently been managed more aggressively by their primary care physicians. Thus, while a randomized clinical trial is absolutely needed, the current study helps answer the question as to whether EBT improves patient outcomes in individuals who seek testing in conjunction with their physician rather than in those offered testing in a clinical research study [29]. The population studied represents how EBT testing is most commonly used now, and perhaps such testing can be more effective than was evident in the study by O'Malley et al. [25]. Nonetheless, a randomized control trial, in an intermediate or high risk cohort, is needed [28].

In summary, our study suggests that EBT coronary calcium measurement may have a role not only in diagnosis of coronary atherosclerosis, but also in improving adherence in patients at highest risk of coronary events. We found that adherence increased in the group who would most likely benefit from lipid lowering therapy, those patients with increased levels of subclinical atherosclerosis. Studies have demonstrated that adherence to therapies such as statin use has led to a decrease in mortality and morbidity. Since the correlation between MDCT and EBT is at worst, reasonable and, at best, excellent [30] it is reasonable to expect that calcium measurement by either modality should improve compliance. Our results as well as the results of previous studies [24,25] suggest that CAC found on EBT may add much needed motivation to asymptomatic patients recommended for lifestyle modification and drug therapy. These promising results will hopefully encourage design of randomized trials to evaluate the improved adherence with EBT [29].

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