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Community-Based Provision of Statin and Aspirin After the Detection of Coronary Artery Calcium Within a Community-Based Screening Cohort

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Objectives We examined the association of coronary artery calcium (CAC) detected on a screening exam with subsequent statin and aspirin usage in a healthy male screening cohort.

Background Whether the presence of CAC, an independent predictor of coronary heart disease outcomes, alters clinical management, such as the use of preventive medications, is unknown.

Methods Men (n = 1,640) ages 40 to 50 years (mean 42 years) were screened for coronary heart disease risk factors and CAC. The CAC scores and risk factors were reported to patients, and results were made available in the electronic medical record; however, medications were not prescribed or recommended by the study. During up to 6 years of subsequent annual structured telephone follow-up, we observed the community-based initiation and persistence of aspirin and statin therapy.

Results A progressive increase in the incidence of pharmacotherapy was noted over time such that those with CAC were 3 times more likely to receive a statin (48.5% vs. 15.5%, $p < 0.001$) and also significantly more likely to receive aspirin (53.0% vs. 32.3%; $p < 0.001$) than those without CAC. In multivariable models controlling for National Cholesterol Education Program risk variables and baseline medication use, CAC was strongly and independently associated with use of either statin (odds ratio [OR] 3.53; 95% confidence interval [CI] 2.66 to 4.69), aspirin (OR 3.05; 95% CI 2.30 to 4.05) or both (OR 6.97; 95% CI 4.81 to 10.10).

Conclusions In this prospective cohort, the presence of coronary calcification was associated with an independent 3-fold greater likelihood of statin and aspirin usage. (J Am Coll Cardiol 2008;51:1337–41) © 2008 by the American College of Cardiology Foundation

Multiple prospective observational studies have shown that coronary artery calcium (CAC) is an independent marker of cardiovascular risk providing incremental prognostic value over traditional and emerging risk markers (1). The incremental value of CAC testing for the detection of coronary heart disease risk has led the National Cholesterol Education Program (NCEP) (2), American Heart Association (3), and American College of Cardiology (1) to include CAC as a candidate component of the coronary risk assessment within published guidelines and expert consensus statements. However, these statements further note that there are no convincing data whether CAC screening alters clinical management (such as the use of preventive medications); thus this remains an important limitation to our understanding the clinical utility of cardiac computerized tomography as a screening test.

In this report, we present the prospective incidence of statin and aspirin usage observed during 6-year actuarial follow-up of the PACC (Prospective Army Coronary Calcium) Project cohort and its relationship to coronary heart disease risk factors and CAC. The principal, pre-specified aim of this analysis was to examine the independent association between CAC and subsequent use of pharmacotherapies to reduce cardiovascular risk.

Methods

This protocol was approved by the Department of Clinical Investigation of Walter Reed Army Medical Center and funded under the congressionally directed, peer-reviewed medical research program of the Department of Defense. Active duty Army personnel (n = 2,000), ages 40 to 50

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Abbreviations and Acronyms

CAC = coronary artery calcium

LDL-C = low-density lipoprotein cholesterol

NCEP = National Cholesterol Education Program

years old, were recruited for cardiovascular risk screening and electron beam computed tomography at the time of periodic, physical examinations as previously detailed (4). Because of the low prevalence of CAC in women in this cohort, this analysis is limited to male participants (n = 1,640). The relationships among CAC, baseline coronary risk factors, and outcomes in the PACC Project have been previously reported (5–7). The finding of CAC in male PACC Project participants has been shown to be associated with an 11.8-fold increased risk for coronary heart disease events during mean 3-year follow-up (8).

PACC project procedures. Each participant at study entry provided details of their medical history, lifestyle behaviors, and psychosocial history, and cardiovascular risk factors were measured (4). Validated instruments were used to assess for habitual physical activity (4,9); diet (10); general functional status; stress; criteria-based DSM-IV diagnoses of depression, anxiety, and somatoform disorders; functional status (11); depression; anxiety; and somatization (12). For the measurement of CAC, electron beam computed tomography was performed with an Imatron C-150 and C300 LXP scanners (Imatron Corp., South San Francisco, California) with the Agatston scoring method (13). A scan was considered positive for CAC when the total CAC score was >0.

Prospective determination of statin and aspirin usage. Medications for the treatment of cardiovascular risk were neither specifically recommended nor provided under the study protocol. Participants were provided with the CAC score and measured risk factor values; however, pharmacotherapy was neither endorsed nor prescribed by the study except for prespecified extreme blood pressure values. After the enrollment visit, participants returned to the care of their primary care providers who determined all subsequent clinical management. The vital status of the PACC Project cohort was tracked through annual telephonic contacts, during which a structured interview was conducted. Data on current cardiovascular health and medications were recorded and medication use was confirmed for completeness through the use of the military's electronic health record. Recorded medications included all commercially available statin medications during the duration of the study and aspirin. Medication usage was classified as either "ever use" or "persistent use." "Ever use" was determined when a participant reported usage of a medication on at least 1 follow-up interview. "Persistent use" was defined as reported use of a medication, once initiated, on all subsequent follow-up contacts.

Statistical methods. The use of medication across time (ever use and persistent use) and the categorical and time-dependent relationships between CAC and statin and/or aspirin were described. We determined the appropriateness of statin use with NCEP guidelines and then stratified the cohort by CAC categories (CAC present or absent). For univariate analyses, continuous variables were compared with a *t* test for independent groups, and categorical variables were compared with the chi-square test. We conducted multivariable logistic regression for the dependent variables "ever use" or "persistent use" of medication (statin, aspirin, or both). Independent variables in this analysis included coronary risk variables as specified by the NCEP, CAC-identified as categorically present or absent, and other variables of interest with possible impact on medication-taking behavior (depression, somatization, education, income). All analyses were performed by expert statisticians (H.W., T.L.) with SPSS for Windows (version 13.0, SPSS Inc., Chicago,

Table 1 Characteristics of the Study Participants

Men, n	1,640
Age (yrs, mean ± SD)	42.9 ± 2.8
Caucasian	71.8%
African American	17.8%
College-educated	82.6%
Cardiac risk factors	
Hypertension	30.8%
First degree of family history for CHD	18.5%
Either first, second, or both degree of family history for CHD	31.7%
Metabolic syndrome	6.6%
Current tobacco use	6.9%
Diabetes mellitus	0.8%
10-yr Framingham risk index CHD	4.6 ± 2.6
10-yr Framingham risk index cardiovascular disease	7.3 ± 3.9
CAC score	
Mean	19.5 ± 110.7
Median	0
CAC score = 0	1,263 (77.6%)
CAC score = 1–9	120 (7.4%)
CAC score = 10–44	120 (7.4%)
CAC score ≥45	124 (7.6%)
Baecke Sports index*	3.0 ± 1.0
Body mass index (kg/m^2)	27.8 ± 3.5
Waist girth (cm)	95.8 ± 24.9
Systolic blood pressure (mm Hg)	124.3 ± 12.0
Diastolic blood pressure (mm Hg)	77.6 ± 8.8
Total cholesterol (mg/dl)	204.2 ± 36.1
LDL-C (mg/dl)	128.5 ± 31.4
HDL-C (mg/dl)	50.4 ± 12.62
Triglycerides (mg/dl)	129.8 ± 86.5
Fasting glucose (mg/dl)	92.7 ± 11.1
Hemoglobin A1C (%) (n = 1,581)	5.4 ± 0.6
Lipoprotein(a) (mg/dl)	30.1 ± 33.5
Homocysteine (μmol/l)	9.6 ± 2.5
Fibrinogen (mg/dl)	315.2 ± 58.9
Insulin (μU/ml)	8.0 ± 6.0
C-reactive protein (mg/l)	1.9 ± 2.2

Values are expressed as mean ± SD. C-reactive protein, n = 832. *Baecke Sports index score ranges from 1 to 5, 5 being most active.

CAC = coronary artery calcium; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

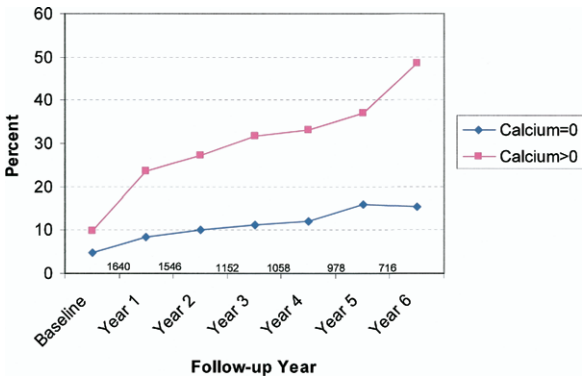

Figure 1 **Incidence of Statin Use During 6-Year Actuarial Follow-Up in the PACC Project Cohort**

Men only; n = 1,640. Ever-use of a statin was noted in 23% of participants, including 48.5% of those with coronary artery calcium and 15.5% of those without coronary artery calcium ($p < 0.001$), which remained significant after controlling for National Cholesterol Education Program risk variables (odds ratio 3.53; 95% confidence interval 2.66 to 4.69).

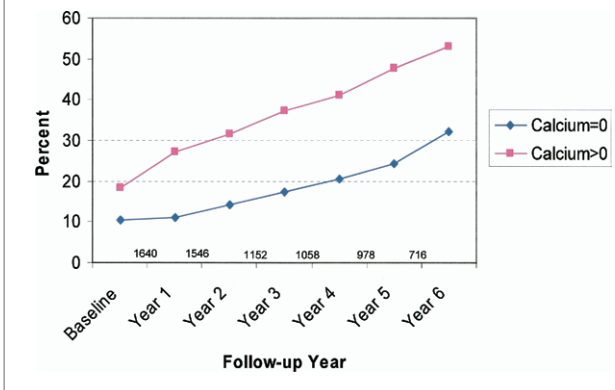

Figure 2 **Incidence of Aspirin Use During 6-Year Actuarial Follow-Up in the PACC Project Cohort**

Men only; n = 1,640. Ever-use of aspirin was noted in 31.2% of participants, including 51.5% of those with coronary artery calcium versus 25.3% of those without coronary artery calcium ($p < 0.001$), which remained significant after controlling for National Cholesterol Education Program risk variables (odds ratio 3.05; 95% confidence interval 2.30 to 4.05).

Illinois). Data are presented as mean ± SD. A 2-tailed p value of ≤ 0.05 was considered statistically significant.

Results

The prevalence of CAC was 22.4% (367 of 1,640) (Table 1). At the time of study entry, the use of statin or aspirin was noted in 94 (5.7%) and 197 (12.0%) participants, respectively. At study entry, those with CAC were significantly more likely to be receiving treatment with statins (9.8% vs. 4.6%; $p < 0.001$) or aspirin (19.6% vs. 9.8%; $p < 0.001$).

During follow-up, subsequent ever-use of a statin was noted in 23% of participants, including 48.5% of those with CAC and 15.5% of those without CAC ($p < 0.001$) with progressive divergence in the incidence of pharmacotherapy over time (Fig. 1). Statin users were significantly different than statin non-users with respect to all major cardiovascular risk variables (Table 2). A similar pattern of aspirin use was noted, with ever-use of aspirin noted in 31.2%, including 51.5% of those with CAC versus 25.3% of those without CAC ($p < 0.001$) (Fig. 2). Aspirin users were significantly different than aspirin non-users with respect to all major cardiovascular risk variables (Table 3). In multivariable logistic regression analysis, the presence of CAC was associated with a 3- to 7-fold greater likelihood of the use of statin, aspirin, or both after controlling for NCEP coronary risk factors (Table 4). These odds ratios were not attenuated after

Table 2 **Characteristics of Participants Stratified by Statin Use Over 6 Years in the PACC Project**

	Never on Statin (n = 1,263)	Statin Users (n = 377)	p Value
Age (yrs)	42.7 ± 2.6	43.4 ± 2.9	<0.001
Prevalence of CAC	16.6%	41.6%	<0.001
Mean CAC score	7 ± 40	59 ± 213	<0.001
Number of NCEP risk factors	1.4 ± 1.0	1.8 ± 1.0	<0.001
Framingham risk score (10-yr)	4.2 ± 2.4	6.0 ± 2.9	<0.001
Body mass index (kg/m^2)	27.6 ± 3.1	28.6 ± 4.5	<0.001
Systolic blood pressure (mm Hg)	124 ± 12	126 ± 12	0.001
Diastolic blood pressure (mm Hg)	77 ± 9	80 ± 8	<0.001
Total cholesterol (mg/dl)	198 ± 33	225 ± 38	<0.001
LDL-C (mg/dl)	123 ± 29	146 ± 33	<0.001
HDL-C (mg/dl)	51 ± 13	48 ± 12	<0.001
Triglycerides (mg/dl)	121 ± 77	160 ± 106	<0.001
Hemoglobin A1C (%)	5.4 ± 0.6	5.5 ± 0.7	0.007

NCEP = National Cholesterol Education Program; PACC = Prospective Army Coronary Calcium; other abbreviations as in Table 1.

Table 3 **Characteristics of Participants Stratified by Aspirin Use Over 6 Years in the PACC Project**

	Never on Aspirin (n = 1,129)	Aspirin Users (n = 511)	p Value
Age (yrs)	42.7 ± 2.7	43.3 ± 2.8	<0.001
Prevalence of CAC	15.8%	37%	<0.001
Mean CAC score	7 ± 38	47 ± 187	<0.001
Number of NCEP risk factors	1.4 ± 1.0	1.6 ± 1.0	<0.001
Framingham risk score (10-yr)	4.3 ± 2.5	5.1 ± 2.9	<0.001
Body mass index (kg/m^2)	27.7 ± 3.7	28.0 ± 3.1	<0.001
Systolic blood pressure (mm Hg)	124 ± 12	126 ± 13	0.001
Diastolic blood pressure (mm Hg)	77 ± 9	79 ± 9	<0.001
Total cholesterol (mg/dl)	202 ± 36	209 ± 37	<0.001
LDL-C (mg/dl)	127 ± 32	141 ± 101	<0.001
HDL-C (mg/dl)	51 ± 13	50 ± 12	<0.001
Triglycerides (mg/dl)	124 ± 78	141 ± 102	<0.001
Hemoglobin A1C (%)	5.4 ± 0.6	5.4 ± 0.7	0.007

Abbreviations as in Tables 1 and 2.

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Table 4 Multivariable Logistic Regression Models Demonstrating the Association of Baseline CAC With Subsequent Medication Usage With and Without Controlling for NCEP Risk Factors

	CAC		NCEP Risk Factors	
Dependent Variable	Odds Ratio	p Value	Odds Ratio	p Value
Statin use	3.53 (2.66–4.69)	<0.001	1.37 (1.20–1.57)	<0.001
Aspirin use	3.05 (2.30–4.05)	<0.001	1.25 (1.10–1.42)	0.001
Statin and aspirin use	6.97 (4.81–10.10)	<0.001	1.52 (1.27–1.82)	<0.001
Persistent use of statin	1.71 (0.97–3.00)	0.06	1.17 (0.89–1.55)	0.26
Persistent use of aspirin	0.80 (0.51–1.27)	0.35	1.07 (0.86–1.32)	0.54

Excluding baseline users of statin and/or aspirin.
Abbreviations as in Tables 1 and 2.

controlling for additional variables including depression, somatization, fitness, diet, income, and education.

We evaluated, among subjects not treated with statins at the time of entry into the study (n = 1,546), the initiation of statin medications during follow-up stratified by baseline NCEP low-density lipoprotein cholesterol (LDL-C) goal status and CAC categories. A total of 469 subjects (30.9%) were not at NCEP Adult Treatment Panel III LDL-C goal at study entry. Among these subjects, the proportion prescribed a statin during follow-up was significantly higher for those with CAC (66 of 110; 55.0%) than those without CAC (108 of 347, 31.1%; $p < 0.001$). Similarly, among subjects with a baseline LDL-C at NCEP goal, a greater proportion received a statin in follow-up (55 of 211; 26.1%) than those without CAC (54 of 868; 6.2%; $p < 0.001$).

The persistence of statin and aspirin use was examined in relation to the presence or absence of coronary calcium. Coronary calcium was not associated with a significantly greater persistence of either medication. Specifically, persistent statin use was observed in 86.6% (136 of 157) with CAC versus 79.1% (174 of 220; $p = 0.06$) of those without. Similarly, persistent aspirin use was observed in 79.4% (150 of 189) with CAC versus 82.6% (266 of 322; $p = 0.36$) of those without. Significant differences in medication persistence were not observed in multivariable analysis after adjustment for the number of NCEP risk factors present or depression, somatization, fitness, diet, income, and education.

Discussion

The PACC Project findings on medication use indicate that the identification of CAC substantially increases the proportion of subjects treated over time with aspirin, statin, or both. These findings from a community-based cohort of nonreferred study participants provide the first demonstration of an independent impact of anatomic-based subclinical atherosclerosis screening on patient management and lend additional support to recent recommendations for use of CAC testing to refine the cardiovascular risk assessment (1–3). Notably this association was incremental to and quantitatively stronger than the association of use of these medications with NCEP risk variables.

Despite these findings, preventive medications were still underused, as previously recognized in both primary and secondary prevention (14). Also, we found increased use of statin among individuals who had achieved their NCEP LDL-C goal, suggesting intensification of treatment beyond that recommended in current lipid treatment guidelines. Although there is interest in CAC identification as a motivational tool, the data to date suggest against an effect of CAC on long-term patient behavior (15). Consistent with this, our study did not find an association between CAC and medication persistence. A motivational effect of CAC is conceptually attractive, but medication persistence is a complex phenomenon determined less by a single health care interaction (a CAC scan) than by numerous factors over time in a longitudinal provider-patient relationship (15–18).

The military health care system is a large closed system of care that provides comprehensive and accessible health care and access to medications without insurance or cost barriers that might influence medication use patterns. The healthy cohort studied herein is notable for several unique characteristics, including generally low coronary calcium scores, high levels of medication persistence, and possibly higher levels of motivation to follow a healthy lifestyle. Although we relied on self-reported medication use, these were identified through a structured medical interview and were verifiable through electronic pharmacy records.

Conclusions

The presence of coronary calcification was associated with an independent 3-fold greater likelihood of statin and aspirin usage and more appropriate use of statins during 6-year follow-up within the PACC Project cohort. These findings support the concept that the identification of coronary calcium in a screening population leads to shifts in clinical patient management reflected in the provision of preventive cardiovascular pharmacotherapies.

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