Reclassification of Patients for Aggressive Cholesterol Treatment: Additive Value of Multislice Coronary Angiography to the National Cholesterol Education Program Guidelines

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ABSTRACT

Background: National Cholesterol Education Program (NCEP) guidelines have been used to define treatment goals in patients with hypercholesterolemia. However, epidemiology-based guidelines are unable to identify all subjects with coronary artery disease for aggressive lipid intervention.

Objective: We sought to evaluate the additive value of multislice computed tomography (MSCT) angiography to the NCEP guideline classification for lipid treatment.

Methods: Multislice computed tomography was performed in 114 consecutive patients (mean age 57 ± 14 y; 59% male) without known coronary artery disease. Subjects were classified into 3 categories (low-, intermediate-, and high-risk) according to their Framingham risk scores (FRS).

Results: Traditional cardiac risk factors were common: hypertension 59%, diabetes 13%, and smoking 22%. On the basis of the FRS, 11% ($n = 12/114$) of the patients met high-risk criteria requiring aggressive cholesterol reduction. Of those in the low- and intermediate-risk groups, MSCT found coronary plaque in 76% ($n = 77/102$), with moderate or severe plaque in 38% ($n = 39/102$), thus reclassifying them in the high-risk category. Use of statin drugs increased from 32% at baseline to 53% ($p = 0.002$) based on MSCT results; statin dose was increased in 31% of the patients who were already on a statin. The mean low-density lipoprotein cholesterol (LDL-c) decreased from 114 mg/dL to 91 mg/dL after MSCT ($p < 0.001$).

Conclusion: Multislice computed tomography reclassifies a high percentage of patients considered to be low- to intermediate-risk into the high-risk category based on their coronary artery lesions. Thus, the rise in MSCT use at present may have a large impact on clinician practice patterns in lipid-lowering therapy.

Key words: tomography, X-ray, computed, risk factors, hypercholesterolemia, practice guidelines

Introduction

National Cholesterol Education Program (NCEP) guidelines have been used to define treatment goals in patients with hypercholesterolemia,¹ mainly by assigning a certain cholesterol target level depending on the Framingham Risk Score (FRS), or the presence or absence of coronary artery disease or its equivalents. However, epidemiology-based guidelines are unable to identify a considerable portion of patients with coronary artery disease for aggressive lipid-lowering intervention. The fact that about half the patients who experience a myocardial infarction have less than 2 cardiac risk factors² suggests that we need more accurate identification of the persons at risk for coronary events.

Multislice computed tomography (MSCT) coronary angiography has recently been introduced as a noninvasive method of detection of coronary atherosclerosis at the individual level. With the advent of 16- and 64-slice scanners, the ability to detect both soft and calcified coronary plaque can be done reliably and with high accuracy.³

Therefore, we sought to evaluate the additive value of MSCT to the NCEP guidelines for lipid-lowering treatment. Specifically, our objectives were as follows: (1) to determine whether low- to intermediate-risk individuals according to the FRS would be reclassified as high-risk based on the detection of coronary artery disease as determined by MSCT, and (2) to assess whether the results from the MSCT would affect physician practice patterns regarding the use of lipid-lowering therapy.

Methods

We identified ambulatory patients seen at the Cleveland Clinic in Florida (Weston, FL, USA), between October 2003 and July 2006 who had undergone MSCT for cardiac evaluation, and in whom clinical variables used for FRS calculation were known. We excluded patients with known coronary artery disease at the time of MSCT. Individual patients' FRSs were computed⁴ taking into account data on age, total cholesterol, high-density lipoprotein cholesterol (HDL-c), diabetes mellitus, systolic blood pressure, and history of

smoking. Patients were classified into 3 categories of 10-y-risk estimates: (1) the low-risk category included patients with <10% probability of developing coronary disease over 10 y; (2) the intermediate-risk category included those with a 10%–20% probability of developing coronary disease over 10 y; and (3) the high-risk category included those with over 20% probability of developing coronary disease over 10 yr. Demographic and clinical data were obtained by database review or from the patients' medical records. Clinical data recorded included history of hypertension; current smoking; history of diabetes mellitus; use of lipid-lowering therapy, specifically a statin drug either at baseline or at follow-up visits; and statin drug dose changes. Complete lipid panels were collected in the fasting state and included low-density lipoprotein cholesterol (LDL-c) and HDL-c levels. Study approval was obtained from our institutional review board and ethics committee.

An MSCT was performed with a Somatom Sensation 16-slice computed tomography (CT) scanner (Siemens, Forchheim, Germany). The protocol included intravenous beta-blockade to a target heart rate of 60 bpm or less, injection of 100 mL contrast substance, and retrospective electrocardiographic gating at the best percentage of the RR interval. Sections of 1 mm with 50% overlap were acquired. Maximum intensity projection was used for reconstruction. We identified plaque as any structure within the coronary artery wall having a different density and being identified in at least 2 planes. Severity of the plaque was classified semi-quantitatively as follows: no plaque if lesion was >25%; mild (25%–49% stenosis); moderate (50%–74% stenosis); or severe (>75% stenosis). According to their degree of calcification, non-calcified plaque were defined as having a density higher than the surrounding tissues but lower than the contrast in the coronary lumen, whereas calcified plaque were identified by a higher density than the contrast. When both types of plaque, calcified and noncalcified, coexisted in the same patients they were labeled as mixed.⁵

Continuous variables were compared using the Student *t* test and proportions using the *z* test for 2 independent group comparisons. For multiple group comparisons, the analysis of variance (ANOVA) and chi-square tests were used and *p*-values of ≤ 0.05 were considered statistically significant.

Results

One hundred and fourteen consecutive patients were identified. Baseline patient characteristics are shown in Table 1. Indications for MSCT were chest pain in 60% (*n* = 68) of patients, evaluation for coronary risk factors in 27% (*n* = 31), and other reasons (including abnormal stress test or planned electrophysiology procedures) in 13% (*n* = 15). According to FRS categories, 69% (*n* = 79) of patients were classified as low-risk, 20% (*n* = 23) as intermediate-risk, and 11% (*n* = 12) as high-risk. Among

the 36 patients who were already on a statin at the time of MSCT, 10 had prestatin lipid panels available. Their FRS changed little after statin use; only 2 patients changed from the intermediate to the low FRS category.

In the total cohort, MSCT found coronary plaque in 76% (*n* = 87) of patients. Moderate and severe plaque were present in 42% (*n* = 48/114) of patients. There was a significant increase in the prevalence of coronary plaque found between the low and the high FRS categories (*p* = 0.043), and between the low and intermediate categories (*p* = 0.03). Coronary plaque detected by MSCT were found in all patients in the high FRS category. In the low and intermediate FRS categories, 68% and 92% of patients had coronary plaque, respectively. Thus, a total of 76% (*n* = 77/102) nonhigh-risk patients were found to have coronary plaque, reclassifying them from low or intermediate FRS to high-risk patients, (i.e., those with coronary artery atherosclerosis) (*p* < 0.001). Among patients with diabetes, 87% (*n* = 13/15) had coronary plaque. If we consider only moderate or severe plaque in order to reclassify patients to the high-risk category, then 38% (*n* = 39/102) of the patients in the low or intermediate FRS category would be reclassified. The prevalence of any coronary plaque and of moderate and severe plaque by the FRS category, and in diabetics, is shown in Figure 1.

Among nonhigh-risk patients with plaque, 49% were mild (*n* = 38/77), 31% moderate (*n* = 24/77), and 20% severe (*n* = 15/77). Among nonhigh-risk patients, 15% (*n* = 15/102) had noncalcified plaque, whereas all high-risk patients had calcified plaque. Among diabetics, 15% had exclusively noncalcified plaque. Categorizing patients based on the original indication for MSCT, coronary plaque was found in 87% (*n* = 27/31) of patients presenting for evaluation of cardiovascular risk, 74% (*n* = 50/68) of patients with chest pain, and 73% (*n* = 11/15) for other indications.

The initial LDL-c level was at goal in 41% (*n* = 5/12) of patients in the high FRS group, 78% (*n* = 18/23) in the intermediate FRS group, and 80% (*n* = 63/79) in the low FRS group; defined by levels of <100 mg/dL, <130 mg/dL, and <160 mg/dL, respectively, according to NCEP/Adult Treatment Panel (ATP) III guidelines. Among the 58 patients who had follow-up lipid levels after MSCT, the LDL-c level was at goal in 100% (*n* = 6/6) of the high FRS patients, 93% (*n* = 14/15) of the intermediate FRS patients, and 92% (*n* = 34/37) of the low FRS patients (*p* = 0.03 for pre-versus post-MSCT LDL-c levels in high FRS category). The average time interval between the initial and the follow-up lipid panel was 397 d. Use of statin therapy in the entire cohort increased from a baseline usage of 32% (*n* = 36/114) to 53% (*n* = 60/114, *p* = 0.002) after results of the MSCT. The statin drug dose was increased in 31% (*n* = 11/36) of patients who were already on a statin drug. Only 1 patient discontinued the statin after a normal MSCT. As seen in Table 2, when new statin use after MSCT was assessed by the FRS category, all

TABLE 1: Baseline patient characteristics

	Overall (n = 114)	Low FRS (n = 79)	Intermediate FRS (n = 23)	High FRS (n = 12)
Age, y*	57±14	53±12	65±12	70±14
Male gender, %*	59	44	100	83
Hypertension, %*	59	41	65	100
Diabetes, %	13	9	27	17
Smoking history, %*	22	16	43	25
LDL-c, mg/dL	114±39	117±42	108±37	121±49
HDL-c, mg/dL	55±15	57±17	53±15	47±6
FRS, %/10 y*	7.2±7.0	3.0±2.2	12.6±2.4	24.9±4.3

* $p < 0.05$. Abbreviations: FRS = Framingham's risk scores; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol.

Figure 1: Prevalence of coronary plaque according to the FRS category and the presence of diabetes.

patient groups demonstrated an increase in statin drug use, although the difference was not statistically significant.

In patients with available pre- and post-MSCT LDL-c levels, measured at least 6 wk after MSCT, the average LDL-c level decreased to 91 mg/dL compared with 114 mg/dL before MSCT ($p < 0.001$). The decrease in LDL-c after MSCT was significant in patients with mild or no plaque (from 127 mg/dL to 113 mg/dL, $n = 13$; $p = 0.02$), and in those with intermediate or severe plaque (from 119 mg/dL to 88 mg/dL, $n = 29$; $p < 0.001$). As seen in Table 3,

new statin use, or an increase in statin use, was significantly more frequent with moderate or severe plaque than with mild or no plaque.

Other preventive measures, which occurred after the MSCT results, were initiation of aspirin usage in 42 patients and of a beta-blocker in 26 patients. Out of 25 active smokers, 6 patients ceased smoking after MSCT. Hemoglobin A1c levels decreased from a baseline of 7.6% to 6.9% ($n = 5$ patients, $p = 0.09$). In 23 patients, an invasive coronary angiogram was performed after MSCT. Among these, 3 patients underwent a coronary revascularization procedure.

Discussion

Our results showed that three-quarters of the patients without known coronary artery disease referred for an MSCT in a general cardiology practice have detectable coronary plaque; more than half of which are moderate or severe plaque. This percentage is similar to the one reported by Hausleiter et al.⁵ in a series of patients with similar baseline characteristics, and is higher than the one reported by Nikolaou et al.⁶ in a series of asymptomatic patients with cardiovascular risk factors, of whom half had coronary atherosclerosis.

More than half of the low and intermediate FRS patients had detectable coronary plaque. The high proportion of coronary plaque in the different FRS categories suggests that further risk stratification can be obtained by noninvasive imaging techniques. This has previously been shown for calcium scoring,⁷ which provides additive prognostic value to traditional cardiac risk modeling. In comparison with calcium scoring CT, MSCT has the advantage of detecting soft noncalcified plaque allowing for earlier detection of the atherosclerotic process. Although most patients had some degree of coronary calcifications, some had only noncalcified plaque that would have been missed by calcium scoring CT, a relevant finding as soft plaque may

TABLE 2: Changes in statin drug use based on FRS category

FRS (%)	Patients	Prevalence of plaque (%)	Baseline statin use (%)	Post-MSCT statin use (%)	Δ (%)
<10	79	60	32	50	+18
10–20	23	80	26	56	+30
>20	12	100	42	75	+33

Abbreviations: FRS = Framingham's risk score; MSCT = multislice computed tomography.

TABLE 3: Changes in statin prescription and LDL-c depending on plaque severity

	Mild or no plaque	Moderate or severe plaque	p-value
New use or increased statin dose	30%	52%	0.04
Decrease in LDL-c post-MSCT	14 mg/dL	31 mg/dL	NS

Abbreviations: LDL-c = low density lipoprotein cholesterol; MSCT = multislice computed tomography.

represent the more vulnerable lesion.⁸ We found exclusively noncalcified plaque in 15% of nonhigh-risk patients, which is consistent with other studies.^{5,6}

In response to the MSCT results, statin drug use increased in all FRS categories with either initiation of drug use or an increase in the current drug dose. The rise in statin drug use is undoubtedly due to a reset in the LDL-c target levels from primary prevention to coronary artery disease equivalent risk levels (i.e., from 130 mg/dL–160 mg/dL to 100 mg/dL or even 70 mg/dL). Another possible mechanism is the effect of the MSCT results on increasing patient (and physician) willingness to aggressively treat hypercholesterolemia, as suggested by the significant increase of at-goal patients in the high FRS group after MSCT. The significant decrease in LDL-c levels observed after MSCT could be an important finding if reproduced on a larger scale. A previous study showed that an abnormal calcium score by electron-beam CT failed to generate a better risk factor control in primary prevention.⁹ Our results suggest that the increase in statin drug use after MSCT is a pattern frequently observed in clinical practice, and the decrease of LDL-c levels would be not uncommonly expected. The findings also showed that the increase in statin prescription and the magnitude of the decrease in LDL-c is greater in those with severe or moderate plaque compared with those with mild or no plaque, suggesting that the change in statin prescription is related to the result of the MSCT rather than other coincidental reasons. The percentage of patients on statins after MSCT may seem low (53%), but is in fact similar to rates achieved after acute coronary syndromes.¹⁰

The main limitation of our study was the presumption that ischemic coronary events are directly related to the presence of coronary plaque by MSCT. There are no conclusive studies to support whether or not the risk of developing manifest coronary artery disease is greater in patients with an abnormal MSCT. This is, for the time being, an emerging dilemma presented by the widespread use of MSCT. The impact of statin drug use on the outcomes of patients with coronary lesions visible by MSCT, but no prior manifest coronary artery disease, is also unknown. There is no evidence regarding improved outcomes based on an MSCT-driven intervention at this time. Prospective work is needed in this direction, and in the absence of outcome data, our study should not imply any benefit of statins in asymptomatic patients with coronary plaque on MSCT.

An additional limitation is related to the retrospective nature of the study and the heterogeneity of the study population. Indications for MSCT included patients with chest pain or abnormal stress tests, and as such, the prevalence of coronary plaque depends on the pretest probability of disease and is expected to be higher in these clinical situations. However, this was unlikely the case in our study, as the prevalence of coronary plaque in patients with chest pain (65%) was similar compared with asymptomatic patients (78%). Although the 16-slice MSCT demonstrated highly accurate qualitative identification of coronary artery lesions, normal for the time when we collected our data, current-day 64-slice scanners offer improved spatial and temporal resolution. This is a technical limitation, which we believe did not significantly alter the overall results of our study. Finally, the results reflected the clinical practice of a single center's cardiology department and may not be applicable to the more general population.

Conclusions

The MSCT reclassifies a high percentage of patients considered to be low- to intermediate-risk by the FRS into patients having atherosclerotic coronary artery plaque. It is unknown if this category of patients have an increased risk of future coronary events. Thus, the current rise in MSCT use may have an impact on clinician practice patterns of lipid-lowering therapy.

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