# Prediction of acute cardiac events in patients with noncalcified plaques using dual-source CT angiography

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## Abstract

Although coronary computed tomography angiography (CCTA) offers a valuable alternative for characterizing nonclacified coronary plaques, its value in evaluating noncalcified coronary plaques after an acute cardiac event (ACE) remains uncertain. *We investigated* the prevalence of ACE and the characteristics of clearly discernible noncalcified coronary plaques using dual-source CCTA. *Forty patients* with noncalcified coronary plaques demonstrated by dual-source CCTA were studied for 7 to 12 months. The prevalence of ACE with a diameter of the stenotic coronary vessel of more or equal to 50% and of less than 50% of the lumen of the stenotic coronary were grouped and compared. The noncalcified plaque was analyzed. *Quantitative CCTA revealed* 29 patients were with ≥50% of diameter stenosis (DS) and 9 of them had ACE; 11 patients were with <DS, 1 of them had ACE. The sensitivity of ≥50%DS in predicting ACE was 31.0% (9/29), with specificity of 90.9% (10/11), positive predictive value of 90% (9/10) and negative predictive value of 33.3% (10/30). The average thickness of noncalcified plaques in patients with ACE (3.4±0.9mm) was larger compared to the plaques in patients without ACE (2.5±0.7mm, P<0.01). *In conclusion*, these data suggest that CCTA plays an important role in evaluating noncalcified plaques. Patients with significant stenoses and thick noncalcified plaques more or equal to 3.4mm in their coronary arteries should be followed up closely.

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## Introduction

Myocardial ischemia is a well-known risk factor to develop acute cardiac event (ACE) in coronary artery disease (CAD) patients [1]. Coronary artery calcium score assessed by electron beam computed tomography (EBCT) or by multislice computed tomography (MSCT) has been used for risk stratification in patients with known or suspected CAD, and the calcium score<100 has been associated with good prognosis to CAD. In addition, the increase in calcium score has shown to be correlated with the rate of ACE [2, 3].

Multislice computed tomography has offered an improved spatial and temporal resolution and provided not only a high diagnostic accuracy in assessing significant coronary artery stenosis [4-6] but also an evaluation on the texture of coronary artery plaques [7-9] and myocardial perfusion defects [10]; Now, with the use of MSCT, clearly discernible noncalcified coronary plaques can be detected in a large group of patients with an intermediate risk for having CAD. The assessment of these plaques by MSCT allows for improved cardiovascular risk stratification [11]. There were significant differences in plaque composition comparing different risk factor profiles and different stages of CAD [12]. A retrospective study showed mixed plaques with a predominantly noncalcified component were correlated with ACE [13]. However, prognostic value of noncalcified plaques for ACE remains uncertain [14, 15]. Plaque rupture, mostly from noncalcified vulnerable plaques, is supposed to play a major role in ACE, and noninvasive techniques are mandatory to stratify the individual risk [16]. In this study, we evaluated the relationship of ACE with discernible noncalcified plaques, using the combined assessment of coronary arterial stenosis and plaque texture, to underline the univariate analysis of the MSCT chracteristics of noncalcified plaques to predict ACE.

## Patients and methods

### Patients

Having obtained the approval from the hospital's ethics committee and the informed consents from the patients, we performed study on selected patients. Inclusion criteria were as follows: 1) suspected CAD as indicated by chest pain complaints, elevated risk profile, such as ECG, blood tests; 2) having no ACE history; 3) having no coronary calcified plaques, if the

patients having calcified plaques, they were excluded from this research; 4) having one coronary noncalcified plaque; 5) plaques were defined as structures ≥1mm$^2$ within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue. All these patients were divided into the following two groups: stenoses with ≥50%DS and <50%DS. These two group patients were followed up for at least 7 months (ranging from 7 to12 months). The types of plaque were classified into the following groups: 1) noncalcified plaques with lower density compared with the contrast-enhanced vessel lumen; 2) calcified plaques with high density; and 3) mixed plaques with noncalcified and calcified elements within one single plaque.

### MSCT

All patients were scanned on a dual-source CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany). Use of nitroglycerin before scanning was based on the physicians' discretion. A bolus of contrast media (Iopromide, 370mg iodine/mL, Shering AG;) was injected into the antecubital vein of each patient, followed by the saline chasing with 40mL to maintain a compact bolus. To reduce the incidence of adverse reaction, proper amount of contrast media and injection speed were determined by the patient's body weight, heart rate, and the scan time. The timing of the acquisition start point was determined by automatic bolus tracking software equipped in the scanner. A pre-scan was performed at the level of the aortic root, and the region of interest was placed within the ascending aorta. The scan was started when the CT density reached above 100 HU. The scan scope was set from the tracheal bifurcation to diaphragm with the following parameters: collimation width 64X0.6mm, rotation time 330ms, tube voltage 120kV, effective tube current 560mA, pitch 0.2-0.4. All images were acquired from the aspiratory phase during the approximately 11s-long breath-hold with simultaneous registration of the patient's electrocardiogram.

### MSCT image reconstruction and plaque evaluation

After the examination, reconstructions in the best diastolic phase (typically 65% of the cardiac cycle) and the best systolic phase (typically 35% of the cardiac cycle) were generated with a smooth or a medium smooth kernel (B25f) automatically. If motion artifacts were observed, additional reconstructions were made in different time points between the R-R intervals. The transverse images were reconstructed with slice thickness of 0.75mm at an increment of 0.5mm.

The coronary artery plaques were observed carefully from both the axial and multiplanar reconstruction images by 2 experienced observers who were unaware of the clinical history of the patients. In case of disagreement, a joint reading was performed and a consensus decision was reached. In each patient, only the noncalcified plaque causing the most serious coronary stenosis was analyzed. The cross-sectional and tangential section of interest plaque was reconstructed. In each patient, on the reconstruction images, the length, thickness and the CT value of the plaque was measured. Three randomly selected regions of interest (≥1.0mm$^2$) were positioned within each plaque and the mean was taken as the CT value. Furthermore, the surfaces (regular or irregular) of plaques was evalued. The regular surface means the surface of the plaque showed smooth, no ulcer or introcession.

### Follow-up

Follow-up information was obtained by either clinical visits or telephone interviews. Hospital records of all patients confirmed the obtained information. Acute cardiac event includes a) cardiac death, b) nonfatal myocardial infarction, c) unstable angina requiring hospitalization, and d) revascularization. Cardiac death was defined as the deaths caused by acute myocardial infarction, ventricular arrhythmias, or refractory heart failure. Non-fatal myocardial infarction was defined based on the criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram [17].

### Statistics

Sensitivity, specificity, NPV, and PPV of MSCT to detect ACE were calculated in the standard way. Continuous variables were described by their means and standard deviations, and were compared with the 2-tailed *t* test for independent samples. Categorical baseline characteristics were expressed as numbers and percentages and were compared between the ACE and without ACE groups using the *chi-square* test. Analysis of variance was compared by the CT mean value, and the length and thickness of the plaque between the ACE and without ACE groups. Statistical analyses are performed using SPSS software (version 11.5) (SPSS Inc, Chicago, ILL, USA) and P values < 0.05 is considered statistically significant.

## Results

The study group was comprised of 40 patients (33 men, and 7 women) mean age 53.5±9.1 years). Significant coronary artery stenosis was detected in 29 patients and 80% of the affected vessels were LAD. The patient data and MSCT plaque characteristics are summarized in Table 1. During a mean follow-up of 11 months (ranging from 7 to 12 months), 10 ACE occurred in 10 patients who underwent coronary revascularization. The percutaneous coronary intervention was performed on 9 patients, while coronary artery bypass grafting was performed on one patient. The sensitivity of ≥50%DS in predicting ACE was 31.0% (9/29), specificity was 90.9% (10/11), positive predictive value was 90% (9/10), and negative predictive value was 33.3% (10/30). In Table 1, the univariate analysis of both clinical and MSCT characteristics to predict events is summarized. There were no statistical differences between the ACE and without ACE groups in the incidence of hypertension, hyperlipedimia, and diabetes mellitus.

Overall, the average thickness of noncalcified plaques in ACE group was significantly higher than that in the without ACE group (3.4±0.9mm and 2.5±0.7mm, respectively, P=0.002, Fig. 1), while no significant differences were observed in length, CT value, or surface smoothness of plaques between ACE and without ACE groups. Based on these findings, we utilized both ≥50%DS and thickness ≥3.4mm to predict the occurrence of ACE. Since 8 patients were found to have non-calcified plaques ≥3.4mm in thickness with ≥50%DS and 6 of them were in the ACE group, the sensitivity was 75% (6/8) with specificity of 87.5% (28/32), positive predictive value of 60% (6/10), and negative predictive value of 93.3% (28/30). Representative MSCT images in a patient with ACE and one without ACE are shown in Figures 2 and 3 respectively. A false-negative result was observed in one

**Table 1.** *Patients' characteristics*

| | Overall (n=40) | ACE (n=10) | Without ACE (n=30) | P value |
|---|---|---|---|---|
| Age (years) | 53.5±9.1 | 54.5±7.7 | 53.2±9.7 | 0.702 |
| Gender (M/F) | 33/7 | 9/1 | 24/6 | 0.484 |
| Hypertension (%) | 18 (45%) | 6 (60%) | 12 (40%) | 0.283 |
| Hyperlipidemia (%) | 3 (7.5%) | 2 (20%) | 1 (3.3%) | 0.087 |
| Diabetes (%) | 3 (7.5%) | 2 (20%) | 1 (3.3%) | 0.087 |
| Stenosis(>/50%/<50%) | 29/11 | 9/1 | 20/10 | 0.160 |
| Diseased vessel | | | | |
| RCA (%) | 7 (17.5%) | 0 (0%) | 7 (23.3%) | 0.097 |
| LM (%) | 1 (2.5%) | 0 (0%) | 1 (3.3%) | 0.570 |
| LAD (%) | 29 (72.5%) | 8 (80%) | 21 (70%) | 0.552 |
| LCX (%) | 3 (7.5%) | 2 (20%) | 1 (3.3%) | 0.087 |
| Plaque | | | | |
| Length (mm) | 9.9±3.2 | 10.5±3.2 | 9.7±3.2 | 0.485 |
| Thickness (mm) | 2.8±0.8 | 3.4±0.9 | 2.5±0.7 | 0.002 |
| CT value (HU) | 56.8±35.6 | 53.7±28.2 | 57.8±38.1 | 0.757 |
| Surface (irregular/regular) | 29/11 | 9/1 | 20/10 | 0.160 |

patient (Fig. 4). The coronary angiography was performed and a stent was implanted two weeks later when no significant stenosis was detected by either MSCT or angiography, but endothelium dissection of LAD was detected using the intravascular ultrasound (IVUS).

## Discussion

Coronary CT angiography is leading a technologic revolution in the field of cardiac imaging. For the first time, it is possible to image the wall of the coronary arteries noninvasively to assess plaque burden, characterize plaques, and assess the degree of stenosis. Though IVUS is the gold-standard for detecting and characterizing plaques, it is limited by its invasive nature and cannot be performed for nonculprit coronary arteries in the routine clinical setting. In our study, patients with <50%DS of coronary artery on CCTA have an excellent prognosis (9.1% event rate), whereas an increased event rate (31.0%) was observed in patients with ≥50%DS.

In order to avoid strong vessel wall calcifications reducing the reliability of image interpretation, we only analyzed the noncalcified plaques. The pathologic examination revealed that all plaques were primari-ly composed of fibrocalcific and necrotic tissues. In common belief, either a large lipid pool or a thin fibrous cap may lead to vulnerable plaques [18]. More comprehensive characteristics of coronary atherosclerotic plaques, which were determined by MSCT images, were presented in terms of plaque components and morphology. Although no significant difference in either CT value or components was detected between these two groups, the morphology showed its own meaning, as reflected by thicker plaques in ACE group as compared to without ACE group. A large-scale study of symptomatic patients with follow-up or consecutive monitoring of plaque progression in animal models may be the solution to find out the true mechanism responsible for plaque rupture.

The prospective evaluation of non-bypassed coronary segments, performed in the CASS (Coronary Artery Surgery Study), showed that only 0.7% and 2.3% of segments with narrowing of <5% and 5%-49% respectively resulted

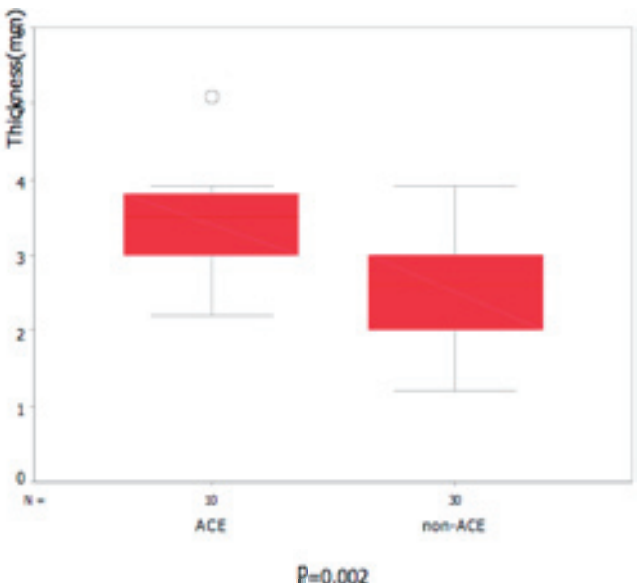


**Figure 1.** The thickness of non-calcified plaques in patients with or without ACE

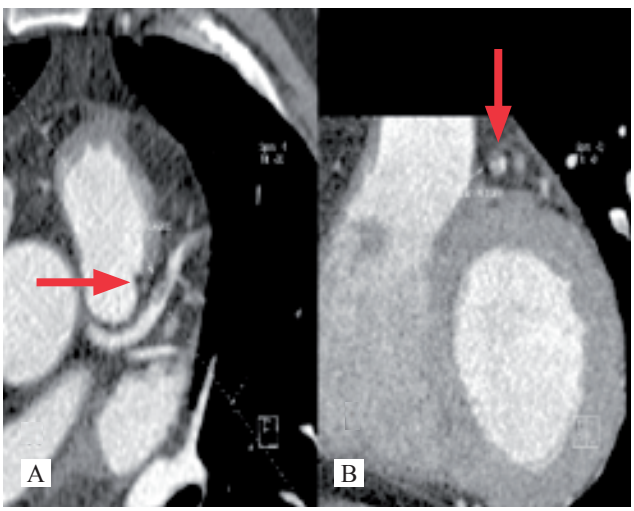


**Figure 2.** Images from a 49 years old man with unstable angina and inversed T wave. Tangential reconstruction image (**A**) showed >50%DS in the LAD (arrow) with an irregular-surface plaque (9.7mm in length and 3.9mm in thickness) and a cross-sectional image of the dash line (**B**) showed high-grade stenosis with a low-density plaque (48 HU, arrow). Coronary angiography demonstrated high-grade stenosis in the LAD and a stent was implanted.

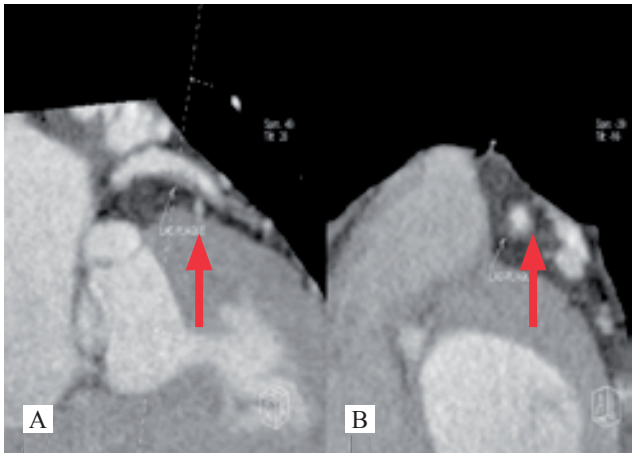


**Figure 3.** Images from a 48 years old man with chest distress. Tangential reconstruction image (**A**) showed <50%DS in the LAD (arrow), with an irregular-surface plaque (9.0mm in length and 2.6mm in thickness) and a cross-sectional image of the dash line (**B**) showed mild stenosis with a low-density plaque (55 HU, arrow).

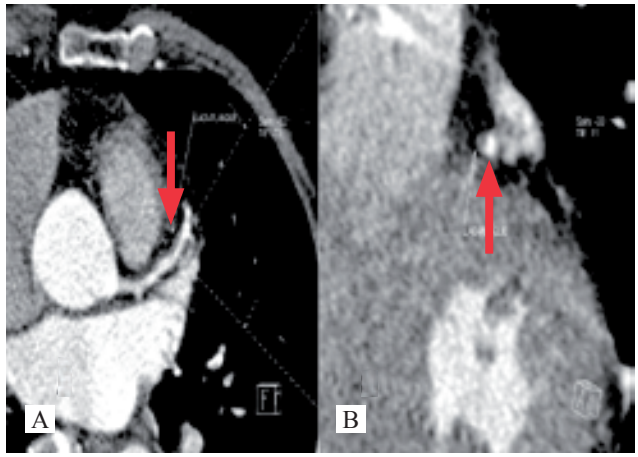


**Figure 4.** Images from a 68 years old woman with unstable angina, hypertension and hyperlipidemia. Tangential reconstruction image (**A**) showed <50%DS in the LAD (arrow) with an irregular-surface plaque (15mm in length and 2.2mm in thickness) and a cross-sectional image of the dash line (**B**) showed mild stenosis with a low-density plaque (83 HU, arrow). Coronary angiography showed no stenosis while intravascular ultrasound showed endothelium dissection of LAD, and a stent was implanted.

in coronary occlusions within a 5-year follow-up study. In contrast, occlusion occurred in 10.1% and even 23.6% of lesions with narrowing 50% to 80% and 81% to 95%, respectively [19]. Our study suggests that the risk of ACE is considerably higher in patients with ≥50%DS, which indicates that these patients were shown to be at the greatest risk for cardiac events. Patients with <50%DS are still at elevated risk as compared with patients without any abnormalities on MSCT. The new idea of our study is to investigate vessel stenoses and plaques' characteristics at the same time, and stratifying the plaque thickness. Moreover, previous studies [15, 18] support the notion that plaque composition (in addition to the extent of stenosis) can predict ACE. The combination of vessel stenosis and thickness of noncalcified plaques can elevate the sensitivity and the negative predictive value, therefore it can be an important factor in predicting ACE. Thus, patients with significant stenoses and thick noncalcified plaques (≥3.4mm) should be followed up closely.

There are some limitations about this study. First, MSCT provides a high diagnostic accuracy in assessing significant coronary artery stenosis, nevertheless, some disadvantages such as cardiac motion artifacts and calcification in the arterial wall reducing the reliability of image interpretation [20, 21] still exist. We excluded calcified plaques from the analysis because the partial volume effect from calcification might lead to the misdiagnosis of stenosis and wrong CT density measurements for the partial volume. However, histological studies have shown that ACE is caused by ruptured, eroded, or spot-calcified plaque [22], and observation suggests that rupture occurs frequently in patients who have acute myocardial infarction and plaques with spotty calcification [23]. To some extent, noncalcified plaques on CT may be not real noncalcified, the $^{18}$F-NaF-PET-CT may provide highly relevant information about the state of molecular calcified plaque before structural calcification is detectable by standard CT techniques [24]. Second, although a culprit lesion is clinically important in the early phase of ACE, a certain number of patients develop plaque ruptures in sites remote from the culprit coronary artery. Thus, detection of rupture-prone, vulnerable coronary artery plaques in the whole coronary artery system is essential for therapeutic decision-making. Exclusion of plaques in non-culprit coronary artery may result in underestimation of the total plaque burden in each patient and reducing the accuracy of predicting ACE. Finally, the study population was limited to a small group and some clinical relevant predictors such as C reactive protein and circulating cytokines were not taken into consideration. Studies in larger cohorts (with longer follow-up) will be required to confirm these initial findings.

*In conclusion*, our study indicates that CCTA can reflect coronary plaque burden, including the severity, extent, morphology, and location of atherosclerosis and it remains as an independent predictor for ACE. The noncalcified plaques in patients with ACE were thicker than those with without ACE patients. The patients with significant stenoses and thick noncalcified plaques (≥3.4mm) in coronary artery should be followed up closely.

*The authors declare that they have no conflicts of interest.*

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