

C O N S U L T A T I O N S I N

Supported by an unrestricted educational grant from
GE Healthcare

C O M P U T E D



www.gehealthcare.com

CONTINUING EDUCATION FOR MEDICAL PROFESSIONALS

T O M O G R A P H Y

To complete this CME activity free of charge, please go to the end of the article for post-test instructions and reader evaluation. Estimated time to complete this activity should not exceed 0.5 hour.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Determine the characteristics of a vulnerable plaque
- Explain the different methods to assess plaque vulnerability
- Describe the benefits of noninvasive imaging using MSCT in the detection of high-risk patients
- Discuss the ability of MSCT to analyze a vulnerable plaque

Who will benefit:

Physicians, physician assistants and radiologic technologists will benefit from the information in this educational activity and can receive Continuing Medical Education credit by completing the post test and evaluation provided.

Assessment of coronary vulnerable plaque using multislice CT

BY ERASMO DE LA PEÑA-ALMAGUER, M.D., FACC

Atherosclerosis is a systemic arterial disease that involves the intima of medium and large systemic arteries, including the carotid, aortic, coronary, and peripheral arteries. It is the leading cause of mortality in industrialized and some developing countries.¹ It has been proven that atherosclerotic disease begins at an early age.² Coronary heart disease accounts for approximately 500,000 deaths each year, and, of the patients who experience myocardial infarction, only about 50% have a history of coronary artery disease (CAD).³

The manifestations of atherosclerotic disease, or atherothrombosis, include such

acute coronary syndromes as unstable angina, myocardial infarction, stroke, and sudden death. Almost 35% of those who suffer a myocardial infarction, which might be the first symptom of atherosclerosis that these patients experience, do not survive due to sudden death.

Most cardiac events are triggered by the rupture of a vulnerable plaque, frequently at nonobstructive locations in the coronary tree.⁴ It has been shown that acute coronary syndromes often result from disruption of an atherosclerotic plaque, which releases thrombogenic components into the bloodstream, leading to thrombus formation and an acute decrease of the luminal diameter, which impedes blood flow around the lesion. Eventually, this will cause ischemia and myocardial electrical destabilization, which, in turn, can lead to life-threatening arrhythmias and cardiac muscle cell necrosis if blood flow is not restored.⁵ It is important to stress the fact that when these plaques heal, they undergo a process known as remodeling, during which chronic deterioration of the

Dr. de la Peña-Almaguer is director of the cardiovascular imaging department at the Christus-Muguerza Heart Institute, Monterrey's University in Monterrey, Mexico, and works with Christus Health USA.

Dr. de la Peña-Almaguer is a consultant for GE Healthcare and MEDIS Medical Imaging Systems. He is also a Speaker's Bureau Member for GE Healthcare.

ASSESSMENT OF CORONARY VULNERABLE PLAQUE USING MULTISLICE CT



Figure 1. Critical lesion in left anterior descending artery in patient with progressive chest pain. Note the minimum amount of calcium and predominant soft plaque component on CT (A). Coronary angiogram (B) and intravascular ultrasound (C) correlation are also shown.

endothelial function occurs.

Having the ability to scrutinize populations at risk noninvasively would theoretically reduce the percentage of patients who suffer sudden death or acute coronary syndromes before symptoms even develop. These patients would then be able to modify risk factors and pay special attention to close follow-up and strict pharmacological and lifestyle modifications.

In the past, practitioners' approach to cardiovascular disease was to determine which patients had symptomatic CAD and treat them with surgical or percutaneous interventions, giving less consideration to atherosclerosis and preventive measures. However, technological advances may, in the near future, allow us to combine clinical risk stratification with noninvasive imaging modalities, such as coronary multislice CT (MSCT), to screen patients at clinically higher risk.

Along with clinical history, physical examination, and biomarkers or noninvasive tests, high-risk patients can be screened at a younger age to assess both their risk and their progress—all at lower radiation doses—and a determination can be made as to which of them should undergo further study.

UNSTABLE PLAQUE, UNSTABLE PATIENT

The definition of unstable or high-risk plaque can be summarized as a plaque

with a high probability of causing local thrombosis. Three types of vulnerable plaques can be identified.

One has a large lipid core covered by a fragile fibrous cap, measures less than 65 μm in thickness, and is prone to rupture. Second is the plaque with superficial erosion, which is also prone to rupture due to the loss of endothelial coverage. This results in direct contact of the underlying connective tissue with the blood, which can lead to thrombus formation. Third, the plaque with a calcified nodule protruding into the lumen is also considered at high risk to induce thrombus due to dysfunctional endothelium surrounding the area and the alteration of blood flow in that region.

The main components of atherothrombotic plaques are connective tissue including collagen, proteoglycans, and fibronectin fibers; crystalline cholesterol, cholesteryl esters, and phospholipids; and cells such as monocyte-derived macrophages, T lymphocytes, and smooth muscle cells; as well as thrombotic material including platelets and fibrin.

The patient at increased risk must be defined. In 2003, Naghavi et al⁶ introduced the term *vulnerable patients*, defining them as “patients in whom disruption of a vulnerable plaque is likely to result in a clinical event” (Figure 1).

Many methods of radiological evaluation, both invasive and noninvasive, are

available to determine which plaques might be vulnerable.

- *Duplex ultrasound.* Widely available, the modality offers adequate information on flow and the size and characteristics of the plaque. However, it is not viable for use in the coronary arteries. Since atherosclerosis/atherothrombosis is a systemic disease, duplex ultrasound has come to be used quite frequently in the carotid arteries, where it can determine plaque size and some characteristics of the plaques. Homogeneous hyperechoic plaques are more fibrous, whereas hypoechoic plaques are associated with a large lipid core.

- *MRI.* Emergence of this technique for evaluating carotid plaques has allowed practitioners to obtain important information on the characteristics of lesions, with a sensitivity of 91% and specificity of 95% for determining the lipid core.⁷ It can also detect fibrous components of plaque, along with the thickness of the fibrous cap, with a sensitivity and specificity of 83% and 81%, respectively.⁸ Technical considerations and availability, however, affect the implementation of this technique for routine clinical use.

- *Quantitative coronary angiography (QCA).* This was one of the first imaging techniques used to serially assess atherosclerotic disease by measuring lumen size. Clinical trials using medications typically demonstrated that treated patients

showed less progression. However, the angiographic differences associated with significantly fewer clinical events were surprisingly small. Cardiovascular events correlate poorly with angiographic lumen size because of characteristics of disease progression: Early on, the vessel expands at the lesion site, allowing the plaque to enlarge without obstructing the lumen. Because of this complex remodeling, angiography underestimates the extent of atherosclerosis compared with post-mortem or intravascular ultrasound (IVUS) measurements and probably with MSCT measurements.

Although obstructive angiographic lesions are a localized disease process, CAD is actually diffuse in essence and widely distributed in the coronary tree. MSCT allows direct observation of a vessel's plaque burden rather than its lumen size.

- **Intravascular ultrasound.** IVUS is an invasive catheter-based technique that provides high-resolution ultrasound images of the lumen and artery wall. If present, the atherosclerotic plaque can be observed and characterized through differences in echogenicity, providing information on the lumen, vessel, and plaque area, and on such morphologic plaque components as lipid core, calcifications, and fibrosis (Figure 1). It is widely used in research centers for the assessment of plaque reduction and in many clinical scenarios to assist in percutaneous coronary interventions.

- **Optical coherence tomography.** OCT is an optical analog to IVUS that measures the intensity of reflected light waves and translates the optical echoes into a high-resolution bidimensional tomographic image. Due to its high spatial resolution—the highest resolution of any vascular imaging modality (ranging from 4 to 20 μm)—it is capable of accurately detecting plaque composition with a sensitivity and specificity for necrotic core size greater than 90%.⁹ Fibrous tissue can be detected with a sensitivity of 79% and specificity of 99%.¹⁰ It is also capable of identifying macrophage infiltration and showing calcified tissue and has a superi-

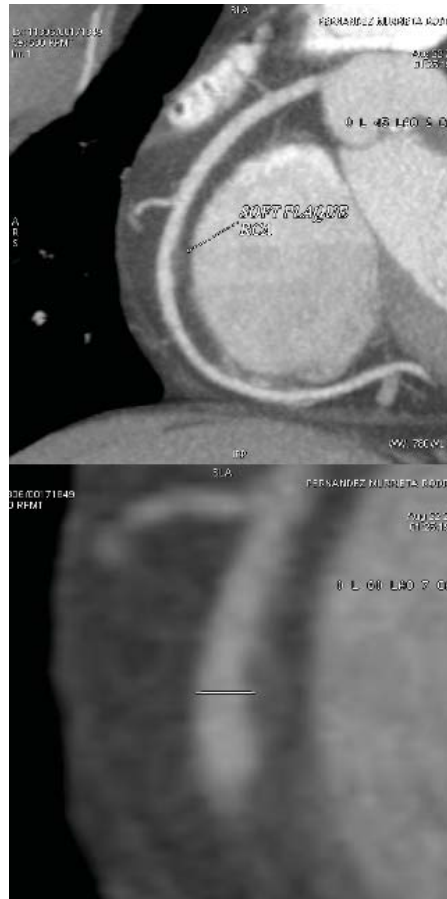


Figure 2. CT images of vulnerable plaque in 28-year-old patient with atypical chest pain and strong family history of heart disease at early ages.

or ability to visualize lipid pools not captured by IVUS.

- **Intravascular elastography ultrasound.** IVEUS is another invasive technique that has been introduced to assess the local mechanical (elastic) properties of the arterial wall. It can accurately diagnose which plaques have such predictors of vulnerability as large lipid cores, thin caps, and heavy macrophage infiltration.

- **Scintigraphy.** Conventional SPECT is limited by its spatial resolution; PET offers a better option for imaging vulnerable plaque. There are a number of radiolabeled markers that can be used to detect inflammation, which may be useful for imaging atheroma. The radiolabeled glucose analog FDG localizes in atheroma at sites of increased macrophage activity in the vasculature and may be suitable to characterize the severity of

inflammation.¹¹ A number of daunting technical hurdles remain, however, before FDG vascular imaging can be applied to routine clinical care.

Following is a partial list of biomarkers and agents that have been suggested for imaging atheroma:

- * lipoproteins
- * low-density lipoproteins labeled with iodine-125, technetium-99m, indium-111
- * oxidized LDL labeled with Tc-99m
- * change of phenotype of vascular smooth muscle cells from contractile to proliferating
- * antibody recognizing a unique epitope on proliferating smooth muscle cells
- * (Z2D3) labeled with Tc-99m
- * inflammation in atheroma
- * glucose utilization of inflammatory cells
- * fluorine-18 FDG
- * apoptosis (primarily caused by toxicity of oxidized LDL in macrophages)
- * Tc-99m annexin
- * increased expression of integrins
- * arginine-glycine-aspartate peptides
- * increased expression of chemotactic factors
- * Tc-99m monocyte chemotactic protein-1
- * increased expression of folate receptors on activated macrophages
- * Tc-99m folate
- **Thermography.** Thermography is a catheter-based technique to detect heat released by activated inflammatory cells within plaques. The difference in temperatures correlates positively with cell (macrophage) density, which may predict plaque disruption. Using this technique, it has been shown that pharmacological interventions can modify the plaque's behavior.¹²

- **Near-infrared spectroscopy.** NIRS measures the reflection signal of near-infrared light to obtain information about the chemical composition of tissue. NIRS may detect the lipid core and features of plaque vulnerability, such as a thin fibrous cap and inflammation. A limitation of this noncontact spectroscopic

ASSESSMENT OF CORONARY VULNERABLE PLAQUE USING MULTISLICE CT

modality is that it is influenced by flowing blood.¹³

- **Intravascular MRI.** An intravascular coil increases the spatial resolution of MR to image plaque in the arteries and discriminate between plaque components, including lipids, collagen, thrombus, and calcium, on the basis of their biochemical properties.¹⁴

MULTISLICE CT

Of the methods currently available to evaluate the anatomical characteristics of a vulnerable plaque, most are invasive. MSCT, with its high spatial and temporal resolution, allows the practitioner to determine coronary obstructions noninvasively. Both in vitro and in vivo studies have determined plaque characteristics. However, no specific target agent or biomarker that will identify an inflamed plaque has been established for use with contrast-enhanced MSCT. In the future, such an agent, used concomitantly with biomarkers, may be able to identify inflammatory cells within a plaque and provide a bull's-eye at which to aim treatment.

MSCT is currently used in two different approaches: coronary calcium score and coronary CT angiography (CCTA).

- **Coronary calcium score.** Initially performed by electron-beam CT and now with MSCT, a coronary calcium scoring is obtained via a non-contrast-enhanced ECG-synchronized scan of the

heart. Using specific thresholds such as calcium volume, Hounsfield units, and density, it generates a score that is then matched to a population percentile according to sex and age. First described by Dr. Arthur Agatston in 1990,¹⁵ it is a great predictor of future coronary events and the presence of obstructive coronary disease.¹⁶

Atherosclerotic lesions go through a series of six stages, which were initially described by Fuster and colleagues.⁵ A plaque's age can be determined by its morphologic and histologic composition. Severe lesions that are associated most commonly with significant luminal narrowing are generally composed of lipids with areas of fibrosis, which corresponds to the later phases of plaque development.

Postmortem studies have identified an unquestionable correlation between coronary calcium and the frequency of myocardial infarction, and clinical outcomes data after coronary angiography have shown a correlation between the severity of the stenosis and the likelihood of future cardiac events.⁴ Although the causes of acute coronary occlusion are multifactorial, destabilization of a plaque and localized inflammation act as precipitating factors for plaque rupture.

It is not yet clear whether calcium functions as a plaque destabilizer facilitating rupture, or whether the presence of calcification signifies plaque maturity and

stability. The latter theory is the one favored by recent research, in which chronic plaque rupture and healing are proposed as the mechanism of calcification.¹⁷

Calcium deposits are found in both stable and unstable plaques; calcified and noncalcified plaques are believed to be present in similar proportions. Coronary calcium score has been postulated as a way to measure the number of soft plaques at a particular site, providing in an indirect, noninvasive way some insight into the likelihood of eventual occlusive coronary disease. However, the absence of coronary calcium does not exclude the presence of CAD, and the higher the calcium score, the more difficult it is to interpret CCTA because of calcium artifacts ("blooming").

- **Coronary CT angiography.** Using small amounts of contrast, injected through an antecubital vein, CCTA is possibly the currently available study that can provide the most anatomical information in the least amount of time. It can distinguish the presence or absence of coronary anomalies, coronary obstructions, plaque composition, right and left ventricular functional parameters, and pulmonary and aortic causes of chest pain and pericardial diseases. Ongoing perfusion trials indicate that this technique will probably become one of the most important tools in the field of cardiovascular disease.



Figure 3. Quantitative coronary angiogram (A), CT (B), and IVUS (D) images of vulnerable plaques in patient with acute coronary syndrome.

PLAQUE CHARACTERIZATION BY MSCT

The ability to determine plaque composition with MSCT has been well documented.¹⁸ Noninvasive, it has high negative predictive value, so is a valuable tool for ruling out cardiac origin of chest pain.

Besides allowing a comprehensive anatomical examination of the heart, MSCT also permits characterization of the lipid, fibrous, and calcific components of coronary plaques that may not be detected in conventional coronary angiography. MSCT detects nonsignificant coronary soft plaques that may be responsible for acute myocardial infarction by providing information on plaque volume, eccentricity, and density at early stages of their formation (Figure 2).

The composition of vascular lesions may be differentiated according to the relative HU densities of calcified versus soft plaques. In general, window levels that differentiate plaque composition are: 30 HU corresponding to IVUS lipid core, and 30 to 150 HU corresponding to IVUS fibrous plaques.

Calcified plaque will have a density of 220 to 500 HU and may be classified as spotty or large calcification. Spotty calcification will consist of plaques less than 3 mm in size surrounded by softer plaques, and large calcification will consist of calcified plaques larger than 3 mm (Figure 3).

MSCT also allows remodeling to be defined, as described by investigators at Massachusetts General Hospital.¹⁶ Results of a study comparing the vascular remodeling of a small group of patients, as identified with MSCT and IVUS, suggested that MSCT offers the possibility to differentiate plaque configuration. The investigators found a strong correlation between tissue density measurements within the plaque and the qualitative ultrasound classifications of soft, intermediate, and calcified.¹⁹

DISCUSSION

Although temporal and spatial resolution

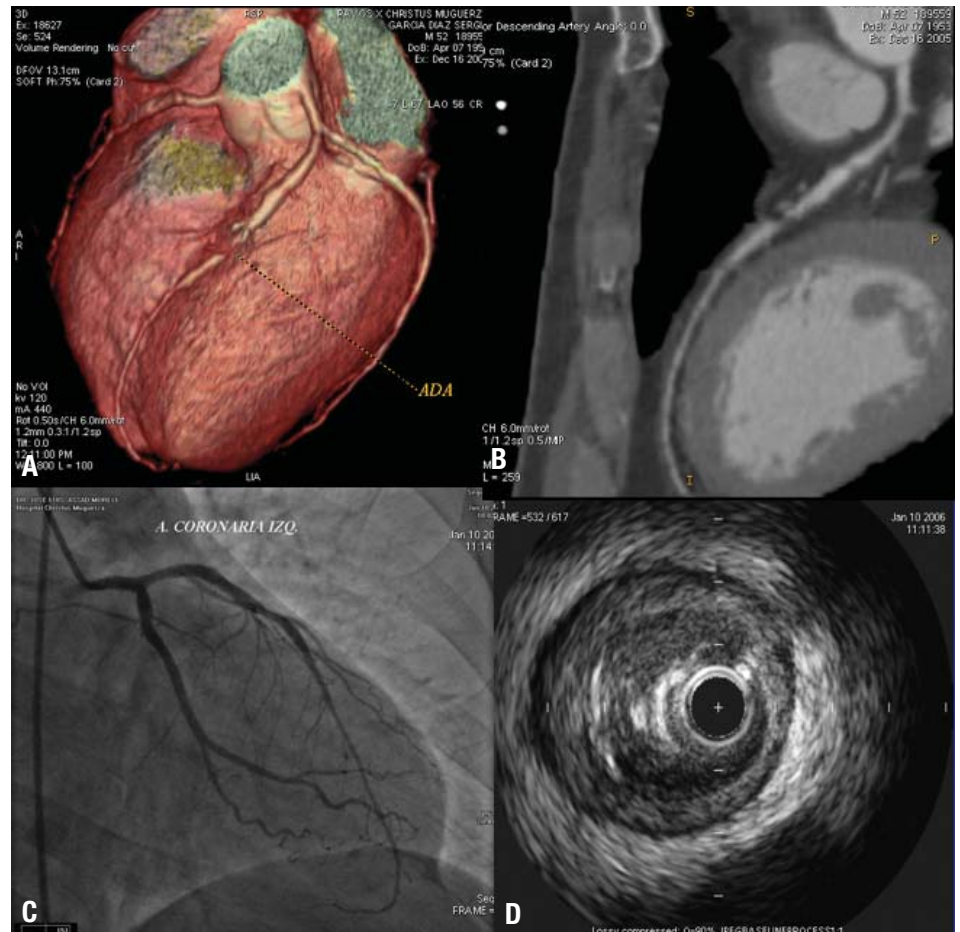


Figure 4. Vulnerable plaque with rupture in patient with acute coronary syndrome. Note correlation between IVUS (D) and CT (A = volume rendered; B = flat) and angiogram (C), which shows only the lumen and not the status of plaque, in characterization of plaque.

are still limited compared with the invasive techniques of IVUS or OCT, MSCT appears to be comparable to the invasive IVUS in characterizing plaque morphology. MSCT might be considered a hybrid imaging method, like merging regular angiography and IVUS. Coronary angiography, despite its limitations, is still the gold standard and the most commonly used method to diagnose obstructive CAD.

The implications and benefits of MSCT compared with IVUS warrant further study, especially of its sensitivity for detecting any type of lesion, specifically vulnerable and moderate or borderline lesions. Such trials should be designed to allow comparison with what is known from already published data using the gold standard regular angiography

(Figure 4).

Ongoing research is looking to establish MSCT's ability to accurately measure plaque burden and differentiate between the plaques' components. In the future, a specific inflammatory biomarker or specific targeted contrast agent may help define not only whether a plaque is vulnerable, but which of the plaques present in a patient's coronary tree are at higher risk for rupture. This will not change the standard clinical approach to patient care, which stresses modifications in diet, exercise, and antistress measures—as well as pharmaceutical interventions including statins and antiplatelet drugs such as aspirin or clopidogrel—in an effort to diminish the inflammatory component of plaque rupture. But it may help clarify when to begin or change such treatment.

ASSESSMENT OF CORONARY VULNERABLE PLAQUE USING MULTISLICE CT

CONCLUSION

MSCT has emerged in recent years as probably the single most important imaging method for the noninvasive assessment of CAD, providing anatomical information not only on the coronary tree but also on ventricular function, wall motion abnormalities, myocardial infarction and its transmural, pericardial disease, other noncardiac causes of chest pain, and the characterization of vulnerable plaque. Ongoing research may help develop agents for myocardial perfusion in the years to come, which will make this technique even more robust. ■

References

1. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;367(9524):1747-1757.
2. Tuzcu ME, Kapadia SR, Tutar E, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults. Evidence from intravascular ultrasound. *Circulation* 2001;103(22):2705-2710.
3. Casscells W, Naghavi M, Willerson JT. Vulnerable atherosclerotic plaque: a multifocal disease. *Circulation* 2003;107(16):2072-2075.
4. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007;50(4):319-326.
5. Fuster V, Moreno PR, Fayad ZA, et al. Atherothrombosis and high-risk plaque. Part I: evolving concepts. *J Am Coll Cardiol* 2005;46(6):937-954.
6. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation* 2003;108(14):1664-1672.
7. Puppini G, Furlan F, Cirotta N, et al. Characterisation of carotid atherosclerotic plaque: comparison between magnetic resonance imaging and histology. *Radiol Med (Torino)* 2006;111(7):921-930.
8. Clarke SE, Beletsky V, Hammond RR, et al. Validation of automatically classified magnetic resonance images for carotid plaque compositional analysis. *Stroke* 2006;37(1):93-97.
9. Yabushita H, Bouma BE, Houser SL, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation* 2002;106(13):1640-1645.
10. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary arterial plaque by optical coherence tomography. *Am J Cardiol* 2006;97(8):1172-1175.
11. Dunphy MP, Freiman A, Larson SM, Strauss HW. Association of vascular 18F-FDG uptake with vascular calcification. *J Nucl Med* 2005;46(8):1278-1284.
12. Stefanadis C, Toutouzas K, Vavuranakis M, et al. Statin treatment is associated with reduced thermal heterogeneity in human atherosclerotic plaques. *Eur Heart J* 2002;23(21):1664-1669.
13. Moreno PR, Lodder RA, Purushothaman KR, et al. Detection of lipid pool, thin fibrous cap, and inflammatory cells in human aortic atherosclerotic plaques by near-infrared spectroscopy. *Circulation* 2002;105(8):923-927.
14. Fayad ZA, Fuster V, Fallon JT, et al. Noninvasive in vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. *Circulation* 2000;102(5):506-510.
15. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15(4):827-832.
16. Hellings WE, Peeters W, Moll FL, Pasterkamp G. From vulnerable plaque to vulnerable patient: the search for biomarkers of plaque destabilization. *Trends Cardiovasc Med* 2007;17(5):162-171.
17. Rudd J, Davies JR, Weissberg PL. Imaging of atherosclerosis—can we predict plaque rupture? *Trends Cardiovasc Med* 2005;15(1):17-24.
18. Pohle K, Achenbach S, Macneil B, et al. Characterization of non-calcified coronary atherosclerotic plaque by multi-detector row CT: comparison to IVUS. *Atherosclerosis* 2007;190(1):174-180.
19. Schroeder S, Kopp AF, Baumbach A, et al. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. *J Am Coll Cardiol* 2001;37(5):1430-1435.

POST-TEST INSTRUCTIONS

To complete this CME activity free of charge, please follow the post-test instructions below: 1. Go to <http://education.CMELLC.com> and login using your e-mail address and password or "register now" if you are a first time user. 2. Click on "CME programs" and "Assessment of Coronary Vulnerable Plaque Using Multislice CT" in the list of programs. To speak to a Customer Service representative, call (800) 447-4474 or (949) 250-1008 (M-F, 7a.m.- 4p.m., Pacific Time). Estimated time to complete this activity should not exceed 0.5 hour.



Release date: 02/26/2008
Expiration date: 03/01/2010
Number of AMA PRA Credits
Designated for this Activity: .50
Item number: M08JS008FEB

To earn AMA PRA Category 1 Credits™ read the article and complete the post test and the evaluation. (Note: A score of at least 75% must be achieved in order to be awarded credit.) The post test will be scored instantly and results will be shown onscreen. You will have the option of printing out a web-generated Statement of Educational Credits Earned. Please make a copy of your test results and your "Statement" for your continuing education records. NO OTHER STATEMENT OF CREDITS EARNED OR CERTIFICATE WILL BE ISSUED.

Please be aware that the accreditation and educational credit information on this web page is current and accurate as of the last update. This may supersede information contained in your printed article.

CME LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CME LLC designates this educational activity for a maximum of .50 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The American College of Radiology (ACR) accepts activities designated for AMA PRA Category 1 Credits™.

Physician Assistants: The American Academy of Physician Assistants (AAPA) accepts AMA PRA Category 1 Credits™ from organizations accredited by the ACCME.

This activity is approved for 0.50 Category A Credits by American Society of Radiologic Technologists (ASRT).