

Angiographic Findings and Clinical Outcomes in Asymptomatic Patients with Severe Obstructive Atherosclerosis on Computed Tomography Angiography

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Abstract

Background: Cardiac computed tomography angiography is a relatively new imaging modality to detect coronary atherosclerosis.

Objectives: To explore the diagnostic value of CTA in assessing coronary artery disease among asymptomatic patients.

Methods: In this retrospective single-centered analysis, 622 consecutive patients underwent CTA of coronary arteries between November 2004 and May 2006 at the Mor Institute for Cardiovascular Imaging in Bnei Brak, Israel. All patients were asymptomatic but had at least one risk factor for atherosclerotic CAD. The initial 244 patients were examined with the 16-slice Brilliance CT scanner (Philips, Cleveland, OH, USA), and in the remaining 378 patients the 64-slice scanner (GE Healthcare, The Netherlands) with dedicated cardiac reconstruction software and electrocardiography triggering was used. Scanning was performed in the cranio-caudal direction. Images reconstructed in different phases of the cardiac cycle using a retrospective ECG-gated reconstruction algorithm were transferred to a dedicated workstation for review by experienced CT radiologists and cardiologists.

Results: Of 622 patients, 52 (8.4%) had severe obstructive atherosclerosis (suspected $\geq 75\%$ stenosis) according to CTA interpretation. Invasive coronary angiography was performed in 48 patients while 4 patients had no further procedure. A non-significant CAD (e.g., diameter stenosis $< 70\%$) was identified in 6 of 48 patients (12%) by selective coronary angiography. Forty-two patients showed severe CAD with at least one lesion of $\geq 70\%$ stenosis. Percutaneous coronary intervention was performed in 35 patients and coronary artery bypass grafting surgery in the other 4 patients. Angioplasty procedures were successful in all 35 patients and stents were utilized in all cases without complications. No further complications occurred among the study cohort undergoing either PCI or surgery. The 6 month survival rate in these patients was 100%.

Conclusions: Non-invasive coronary CTA appears to be a reliable technique, with reasonably high accuracy, to detect obstructive atherosclerosis in asymptomatic high risk patients for atherosclerotic CAD.

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The non-invasive characterization and quantification of atherosclerotic plaque burden may have important implications for the prevention of coronary artery disease progression and its complications [1]. Conventional invasive coronary angiography

still remains the reference standard for diagnosis of CAD and detection of coronary artery stenosis. Despite the invasiveness and possible related complications of ICA, it is vital for guiding interventional or surgical treatments. However, in certain clinical situations, the comprehensive assessment of obstructive and non-obstructive CAD may eventually increasingly rely on non-invasive imaging techniques [1,2].

Coronary computed tomography angiography has recently been introduced as a method for non-invasive visualization of coronary artery stenosis [3]. Leschka and co-workers [4] first reported the diagnostic accuracy of 64-slice CT in assessing coronary artery stenosis in comparison with ICA. Recent studies have reported excellent diagnostic accuracy of 64-slice CT in detecting significant stenosis in symptomatic/high risk patients [5,6]. Few studies have compared the degree of stenosis detected by 16 or 64-slice CT [7,8]. The two methods appear to be moderate, even for selected segments with high image quality. CTA also permits visualization of coronary atherosclerotic plaque and degree of calcifications [9].

The diagnostic accuracy of CTA and its prognosis in patients with known or suspected CAD is well established [10]. However, most of those studies were conducted with a very specific subset of symptomatic patients who had a high prevalence of CAD and who were already scheduled for ICA. Moreover, severe calcification reduces the ability to detect stenosis in the calcified segment and remains an important limitation of this technology.

There are no established indications or guidelines to direct the appropriate evidence-based management of those patients with significant obstructive atherosclerotic coronary findings but no ischemic symptoms. A recent scientific statement from the American Heart Association also does not recommend using CTA as a screening test for atherosclerosis in asymptomatic patients since there is limited information showing the benefit of revascularization in terms of prolongation or quality of life in such patients [11,12]. However, it is likely that non-invasive coronary CTA will eventually be necessary for the routine examination of asymptomatic or minimally symptomatic patients with moderate risk [1]. CTA is currently of uncertain value in the evaluation of asymptomatic patients with risk factors for CAD. In addition, data on the outcome of patients referred for invasive diagnosis and revascularization treatment following CTA are sparse. Therefore,

CTA = computed tomography angiography

CAD = coronary artery disease

PCI = percutaneous coronary intervention

ICA = invasive coronary angiography

the purpose of the present study was to assess the accuracy and clinical outcomes of asymptomatic patients with risk factors for atherosclerotic CAD who were diagnosed as having severe obstructive atherosclerosis by CTA examination and subsequently underwent a cardiac catheterization procedure and possible intervention.

Patients and Methods

This retrospective single-centered analysis was carried out from November 2004 to August 2006 at the Mor Institute for Cardiovascular Imaging in Bnei Brak, Israel. Of 622 consecutive patients who were screened with CTA, 52 were recruited for the study. All participants were asymptomatic and were self-referred to a CTA examination. The patients had at least one risk factor for atherosclerotic coronary disease (family history of symptomatic CAD, hypercholesterolemia based on total cholesterol > 200 mg/dl and/or low density lipoprotein-cholesterol > 130 mg/dl, current or previous smoking history of > 1 year, diabetes mellitus or hypertension on pharmacology treatment, and/or peripheral vascular disease). Patients were excluded if they presented with irregular heart rate, allergy to contrast medium, bronchial asthma, and impaired renal function (creatinine level > 1.4 mg/dl or creatinine clearance < 60 ml/min). All eligible patients provided signed written informed consent before the examination and after receiving a full explanation about the procedure. All patients underwent a detailed medical examination by an internist prior to the CTA examination. Three hours before the examination, oral beta-blockers (either metoprolol 50 mg or propranolol 20 mg) were given to all patients who were not already taking this class of medications. To facilitate adequate breath hold, the patients were connected to an oxygen mask and asked to briefly hyperventilate.

CTA scan protocol

The initial 244 patients were examined with the 16-slice Brilliance CT scanner (Philips, Cleveland, OH, USA) and the remaining 378 patients with the 64-slice scanner (GE Healthcare, The Netherlands) with dedicated cardiac reconstruction software and ECG triggering. All patients were placed in a supine position for the examination. First, a native scan without the contrast medium was recorded to calculate the calcium score. Then, by using a single head power injector (Envision CT, Medrad, Indianola, PA), 100–120 ml (16-slice imaging) and 80 ml (64-slice imaging) intravenous non-ionic contrast material (Ultravist 370, Schering AG, Germany) were injected at a rate of 4 ml/sec into the antecubital vein without a saline flush. The time to peak arterial contrast enhancement was calculated using designated software. The scan volume was determined from the apex of the lungs to 2–3 cm below the diaphragmatic surface of the heart. The CT scan began at the aortic root, cranial to the coronary ostia and stopped at the diaphragm, caudally of all cardiac structures. Scanning was performed in the cranio-caudal direction, using 140 KV, 400 mAs, 0.4 sec rotation speed, and 64 x 0.5 mm detector array. Slices were at 1 mm collimation with 50% overlap. Pitch, which was dependent on the heart rate, averaged 0.3.

Invasive angiography and further interventions

ICA was indicated in some of the patients with severe stenosis. Following ICA, percutaneous coronary intervention or coronary artery bypass graft was recommended. All the patients undergoing PCI were instructed to take clopidogrel for 3–12 months following the procedure, in addition to aspirin. All patients were contacted by telephone at 6 months for clinical outcome.

CTA image reconstruction

Images were reconstructed in different phases of the cardiac cycle using a retrospective ECG-gated reconstruction algorithm with 1 mm-thick sections and reconstruction of 0.4 mm. All images were transferred to a dedicated workstation for review by one of the three experienced CT radiologists and were further reviewed by one of the two experienced cardiologists.

CTA data analysis

All images were transferred to a workstation with dedicated cardiac reconstruction software (GE Healthcare) for review in a blinded manner by two experienced CT radiologists, by consensus. The initial retrospective ECG-gated reconstruction was generated with the reconstruction window, starting at the end-diastolic phase (i.e., 70% of the R-peak interval). When the data were insufficient because of motion artifacts, additional reconstruction data were obtained in increments and decrements of 10%. All segments ≥ 2 mm in diameter belonging to the left main, left anterior descending, left circumflex, and right coronary arteries were included, according to the modified classification of the American College of Cardiology/American Heart Association. The images were evaluated by axial scans, curved multi-planar reformations through the lumen of the coronary vessels, and three-dimensional volume-rendered visualization. In accordance with established cardiology practice, the minimal diameter of stenotic coronary lesions was measured with manually positioned electronic calipers and compared with the maximal diameter of the closest proximal normal arterial segment. Segments were graded as normal, non-obstructed (< 50% luminal stenosis), or obstructed (> 50% luminal stenosis). The latter group was further categorized as moderately obstructed (50–75% stenosis) and severely obstructed (> 75% stenosis). Stenoses of $\geq 75%$ of the diameter were considered indicative of significant CAD. The latter group was referred for further angiographic evaluation and possible intervention.

Data misinterpretation

In 1 of 22 patients (4.5%) the study was not interpretable due to either high (i.e., > 1000) calcium score, heart rate variability and/or false contract injection technical errors. This yielded a total additional 28 patients with unsuccessful study attempt who were not included in the current analysis. The same analysis per vessel yielded a total of 1/17 vessels (5.8%) that were not interpretable due to similar procedural limitations and/or errors. This figure may underestimate the true procedural misinterpretation rate since we can not assure for tracking all existing anatomical seg-

ments, especially in myocardial regions of small branching and/or distal segments.

Coronary artery calcium score

ECG-gated calcium was scored according to the Agatston method [13] to quantify the amount of calcification in the coronary arteries. A focus of coronary calcium was defined as the presence of four or more contiguous pixels with > 130 Hounsfield units. The total calcium score was calculated from the sum of the individual scores of the four major epicardial coronary arteries.

Invasive coronary angiography

Coronary angiograms were recorded at baseline and after PCI using the MDView™ QCA System (Medcon Telemedicine Technology-McKesson, Tel Aviv, Israel). The contrast-filled guiding catheter (6 or 7 French) was used as calibration standard. Reference and minimal lumen diameter was determined before and after PCI. Standard morphological criteria were used to identify lesion location, lumen diameter, and stent length and thrombus. Based on these measurements, percent diameter stenosis was determined before and after intervention. TIMI flow grade (0 to 3) was measured prior to and at completion of the procedure. Procedural success was defined as residual stenosis of < 30% within optimal distal flow and without residual dissection or perforation.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as number of patients (n) and frequency of patients (%).

Results

Baseline characteristics

According to CTA examination, 52 of 622 patients (8.4%) were found to have severely obstructive atherosclerosis (≥ 75% stenosis). Forty-eight patients eventually underwent coronary angiography. Medications and risk factor management alone were prescribed for four patients. Of those 48 patients, 87% were males. Mean age for the group was 57.8 ± 12.2 years. Other baseline demographic characteristics of these 48 patients are given in Table 1.

Table 1. Baseline demographic and clinical parameters of patients who underwent CTA followed by ICA

	N=48
Demographics	
Males	87% (42)
Age in years	57.8 ± 12.2
Risk factors	
Smoking history	25% (12)
Diabetes	10% (5)
Hypertension	39% (19)
Hypercholesterolemia	60% (29)
Family history of coronary artery disease	64% (31)

Data expressed as mean ± SD

Data expressed as % of patients; (n)

Table 2. CTA details and lesion characteristics for patients undergoing ICA

	N=48
Obstructive atherosclerosis (≥ 70% stenosis)	100% (48)
Type of disease	
Single vessel disease	58% (28)
Double vessel disease	33% (16)
Triple vessel disease	8.3% (4)
Target vessels	
LAD	64.5% (31)
RCA	25% (12)
LCX	10.5% (5)
Type of plaques	
Calcified plaque	50% (24)
Soft plaque	23% (11)
Mixed calcified and soft plaques	27% (13)
Type of atherosclerotic disease	
Local	40% (19)
Diffuse	60% (29)
Mean calcium score	184 ± 432 (range 0–1280)

LAD = left anterior descending artery, RCA = right coronary artery,

LCX = left circumflex artery.

Data expressed as mean ± SD

Data expressed as % of patients; (n)

Calcium score, range 0–1280

Detection of coronary artery stenosis

A non-significant angiographically CAD (e.g., diameter stenosis < 70%) was identified in 6 of 48 patients (12%) by selective ICA. Findings from CTA are shown in Table 2. According to CTA, of the 48 patients who underwent ICA, 28 (58%) had single vessel disease, 16 (33%) had double vessel disease, and 4 (8.3%) had triple vessel disease. Calcified plaque was presented in 50% of the patients while the rest had either soft (23%) or mixed calcified and soft (27%) plaque. Local atherosclerotic disease was demonstrated in 19 patients (39%), while 29 (60%) demonstrated diffused disease. Mean calcium score was 184 ± 432. In most of the cases, LAD including major diagonal branches was the culprit artery (64.5%).

Recommendations following CTA examination

Pharmacological management was initiated in 42 patients (87%) (e.g., initiation or dose escalation of statin drugs in 67% and aspirin in 56% of patients) based upon the CTA findings. Complementary exercise testing was recommended in 8 patients (17%) and 6 (12%) were instructed to undergo single photon emission computed tomography imaging prior to angiography. Of the six patients, five patients had some notable ischemic findings on SPECT imaging.

LAD = left anterior descending artery

SPECT = single photon emission CT

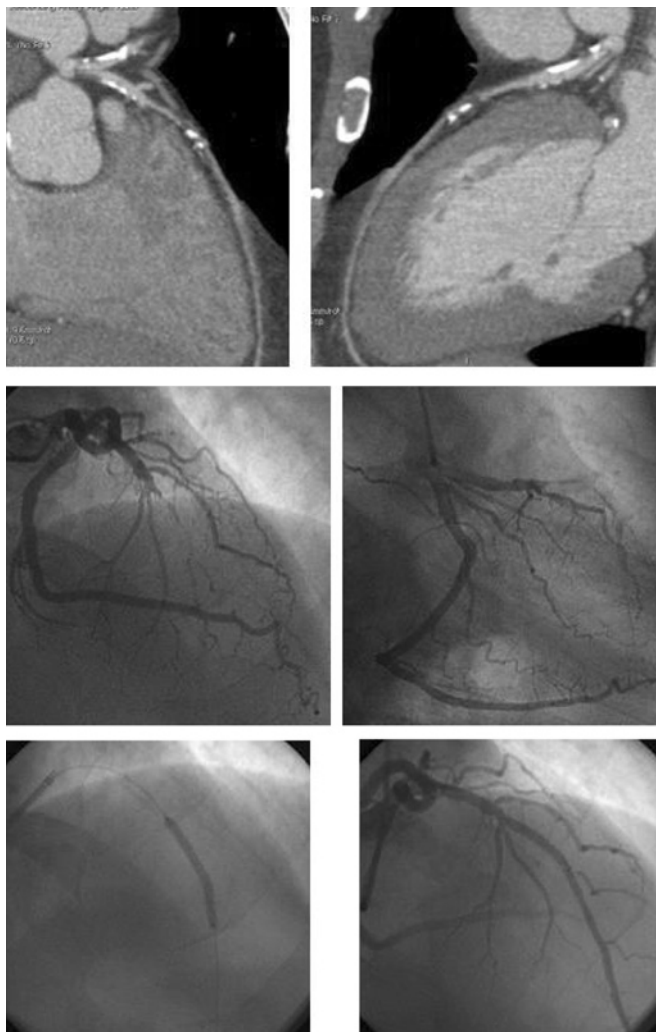


Figure 1. Critical LAD stenosis according to CTA interpretation (upper panel) revealed as total LAD occlusion using “invasive” angiography (middle panel) and undergoing successful stent-based PCI procedure (lower panel).

Comparison of results with CTA and ICA

Selective ICA revealed a non-significant angiographic CAD disease (e.g., diameter stenosis < 70%) in six patients. Four of these six patients had severe coronary calcifications according to CTA, with a mean calcium score of 423 ± 322 . Among the other 42 patients, there was angiographic evidence of severe CAD with at least one lesion severity of $\geq 70\%$ by visual estimation detected in 42 patients. This exhibited an agreement of coronary severity in 88% of studied patients in our series between invasive angiography and CTA. Total occlusion was found in three patients by ICA, of whom two were already diagnosed using CTA, whereas the third patient was diagnosed with a 75–90% mid-LAD lesion while the actual stenosis was characterized by

100% total occlusion [Figure 1]. This latter patient underwent a successful stent-based PCI procedure.

There was one additional lesion discovered in the angiogram in 3 patients (6%) that was either missed or underestimated according to the CTA examination. Figure 2 provides a case example of suspected severe coronary atherosclerosis by CTA detection that was revealed to be a non-significant minimal angiographic lesion (i.e., false positive interpretation).

Further revascularization procedures

Of these 42 patients 39 underwent coronary revascularization procedures: PCI in 35 and CABG surgery in 4. The revascularization rate in the study group with severe angiographic stenosis (by ICA) was 93%. Angioplasty procedures were successful in all 35 patients and stents were utilized in all cases without complications. Three patients, despite having obstructive lesions, were treated conservatively according to the operator's discretion.

Clinical outcomes

All patients were followed for 6 months. Among the 622 patients originally studied with CTA, 39 (6.3%) eventually underwent revascularization procedures. The 6 month survival rate was 100%. One patient who underwent CABG surgery sustained a mild post-pericardiotomy syndrome and was treated medically. No further complications occurred in the study cohort undergoing either PCI or surgery.

Discussion

According to our findings, non-invasive cardiac CTA can accurately reveal severe CAD among asymptomatic patients with atherogenic risk factors. Although previous studies examined the significance of calcium score in asymptomatic patients [14], to the best of our knowledge the present study is one of only a few reports to evaluate exclusively asymptomatic patients who underwent CTA evaluation with the recently developed multi-slice CTA. In a recent study [15] using a 16S machine in 244 asymptomatic patients, we identified no atherosclerosis in 108 patients (44.3%), mild or moderate non-obstructive disease (< 50% stenosis) in 124 patients (50.8%), and significant obstructive coronary artery disease (> 50% luminal stenosis) in 13 patients (4.9%).



Figure 2. A representative case of a presumably significant proximal LAD stenosis by CTA (left) that had < 50% stenosis using invasive angiography (right).

This study demonstrates the accuracy and overall clinical performance of CTA in asymptomatic patients with high risk factors for atherosclerotic CAD who were diagnosed as having severe obstructive atherosclerosis according to CTA examination and subsequently underwent cardiac catheterization procedure and possible intervention. Our study shows good correlation between CTA and catheterization regarding lesions found in asymptomatic patients with risk factor(s). In our study, we found a high sensitivity and specificity as well as high negative predictive value for the detection of coronary artery stenoses by CTA in a group of 48 consecutive asymptomatic patients with high risk for atherosclerotic CAD. The management of asymptomatic patients with a risk factor for atherosclerosis is controversial. Many guidelines have been developed concerning the use of non-invasive testing to screen for asymptomatic coronary disease [16,17]. Recent technological developments have made non-invasive imaging of the coronary arteries possible. The use of non-invasive testing – such as exercise testing, stress echocardiography and myocardial perfusion imaging – is probably offered for selected patients with a possible need for risk factor modification or interventional procedure for primary prevention [18].

The use of CTA has launched a new era in the diagnosis of coronary atherosclerosis. With the last generations of multi-slice CT, a high level of accuracy in detecting coronary artery stenosis was achieved as compared to invasive coronary angiography. Recent findings indicate that CTA demonstrates significantly higher sensitivity and specificity than myocardial perfusion imaging in detecting significant coronary artery disease. CTA accuracy evaluation studies found sensitivities ranging from 83% to 99%, specificities ranging from 93% to 98%, and remarkably high negative predictive values from 95% to 100% [19-21]. In another study of 144 patients with intermediate likelihood of coronary artery disease who underwent a head-to-head comparison between CTA and myocardial perfusion imaging it was found that in patients with obstructive CAD on CTA, 50% of patients had a normal myocardial perfusion imaging [21]. Thus compared with other imaging modalities, cardiac CTA has better imaging capabilities for the evaluation of coronary artery disease in symptomatic and asymptomatic patients [8]. These findings suggest a potential important role of coronary CTA for reliably ruling out severe CAD in the large patient population with equivocal presentation and who currently undergo invasive workup for exclusion of the remote possibility of stenotic CAD. Another study by Rispler et al. [22] assessed the physiological significance of coronary artery lesions using SPECT imaging in accordance to a hybrid interpretation of SPECT with a 16S CTA in patients sustaining chest pain. In 170 coronary evaluated segments, the sensitivity, specificity, positive predictive and negative predictive values were 96%, 63%, 31%, and 99%, respectively, as compared to 96%, 95%, 77%, and 99%, respectively, for SPECT/CTA. Thus, hybrid SPECT/CTA imaging may result in improved specificity and positive prediction to detect hemodynamically significant coronary lesions in patients with chest pain.

Recently, the American Heart Association Writing Group evaluated the application of CTA in different clinical scenarios

with respect to many different studies [24]. Most of the studies focused on symptomatic patients, especially those suffering from chest pain. There was yet no significant follow-up evaluation of patients without symptoms who are diagnosed with significant stenosis by CTA.

Our results show an overestimation of coronary obstruction severity in 12% of our study cohort by CTA. This was mainly due to severe calcifications at the lesion site in four of six cases. Overestimated interpretation due to a calcium "blooming" effect was more common using the 16S CTA machine. Thus, using state-of-the-art methods and evaluation algorithms could result in good correlation of stenosis severity between the software-assisted CTA evaluation and the results of the coronary catheter angiography. This is probably due to superior temporal resolution of the 64S machines [21-23]. In the investigation by Schuijf and co-workers [24], the subset of the agreement between invasive angiography and CTA among patients undergoing both procedures was excellent (90%), and similar to our results. In our study, total occlusion in two of three patients was accurately identified by CTA. Additionally, the revascularization rate in our study group following ICA was 93% and the 6 month follow-up of these patients was event free. Therefore, the concern that non-invasive evaluation of asymptomatic patients could lead to inappropriate or unnecessary diagnostic testing and interventions is real and probably should stress the need for improved modes of screening patients prior to their undergoing CTA, which is associated with radiation exposure and cost.

Limitations

In the selected group of asymptomatic patients with some risk of CAD, but not preexisting CAD, that we included in our study, CTA seems to be able to reliably detect occult atherosclerosis. Nonetheless, the fact that only 8.4% of screened patients had significant CAD on CTA suggests the inclusion of a larger proportion of low risk asymptomatic subjects rather than intermediate to high risk asymptomatic patients. This is probably due to the self-referral nature of our patient cohort.

In our series, we recommended catheter-based angiography based on the severity of CTA findings in most cases, regardless of establishing the diagnosis of coexisting myocardial ischemia. Thus, a major limitation of our study is that there was no comparison to other accepted methods for screening such as exercise test or other imaging methods. It should be emphasized that the use of CTA in this study is currently not recommended by the American Heart Association, the European Society of Cardiology, and/or Israeli guidelines (e.g., use in asymptomatic persons and without detection ischemia). Although our results are promising, it appears that every patient who underwent revascularization was also of doubtful 'classical' indication for stenting or bypass surgery, without symptoms of heart disease. Thus the entire experience may be criticized for revascularizing asymptomatic persons. The policy to proceed with revascularization procedures was left to the clinical judgment of the operators who performed the catheterization procedure. We acknowledge that our study can not establish 'proof of concept' concerning the optimal

management of these patients with severe occult coronary atherosclerosis, as we recognize that those patients could, as well, be followed conservatively and treated using risk management and pharmacotherapy alone. Although our study does seem to reflect the current tendency to use CTA as an initial screening strategy and a decrease in perfusion imaging or even ischemia testing, the evidence for this approach is lacking. It remains to be seen whether it compares favorably to a more traditional risk stratification based on the assessment of risk factors and clinical or objective signs of myocardial ischemia. Moreover, the use of CTA in asymptomatic subjects as a guide to an invasive treatment strategy involving selective coronary angiography and then revascularization in 93% of patients with significant CAD could be judged much more critically. Indeed, there is no proof that these patients benefit from this approach in the long term and a 6 month follow-up is by no means sufficient to support its use. Recent data from the COURAGE study actually proposed that conservative management might be a suitable approach instead of coronary angioplasty for selected patients at relatively low to moderate risk for future cardiovascular events [25].

Additional limitations of coronary CTA scanners include the exposure to radiation, the use of contrast and the need for beta-blocker pharmacotherapy to reduce the heart rate. Finally, in our analysis the number of patients examined with 16-slice and 64-slice machines is not equal. Although we could not control this breakdown of cases in our series we believe that larger studies are needed using the most up-to-date equipment (e.g., 64-slice machine or even higher).

Conclusions

Non-invasive cardiac CTA can accurately detect severe coronary disease among asymptomatic patients with atherogenic risk factors. Future studies should lead to indications that are more specific and/or guidelines concerning which patient should be evaluated by CTA, a decision with immense medical and economic consequences.

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