Predictive Value of Adiponectin in Patients with Multivessel Coronary Atherosclerosis Detected on Computed Tomography Angiography

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Aim: Multislice computed tomography coronary angiography (CTCA) can be used to detect coronary plaques that predict the risk of cardiovascular events. This study aimed to identify the risk factors associated with the extent of coronary plaques detected using CTCA and to determine the value of adiponectin measurement for identifying high-risk patients with multivessel coronary atherosclerosis.

Methods: The study included 298 patients who underwent CTCA for coronary artery disease (CAD) screening between July 2008 and October 2011. We investigated the relationship between the extent of coronary atherosclerosis in terms of the number of diseased vessels and various risk factors, including the serum adiponectin level.

Results: The adiponectin level was found to be significantly associated with multivessel coronary atherosclerosis in a univariate analysis \( (p=0.001) \). A multivariate analysis revealed the adiponectin level to also be significantly associated with multivessel coronary atherosclerosis \( (p=0.01) \), independent of other significant risk factors, including an advanced age, male gender, diabetes mellitus (DM) and hypertension (HT). A receiver operating characteristic curve analysis revealed that a combination of these factors significantly predicted multivessel coronary atherosclerosis (area under the curve, 0.73; 95% confidence interval, 0.67-0.78). As the number of these factors increased, the proportion of patients with multivessel coronary atherosclerosis increased, while the proportion of patients with normal coronary arteries decreased \( (p<0.0001) \).

Conclusions: A low adiponectin level combined with an advanced age, male gender, DM, and HT is independently and incrementally associated with multivessel coronary atherosclerosis. The number of factors may predict the extent of coronary atherosclerosis in patients without documented CAD.

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suggests that the aggressive use of this therapy in addition to improvements in the selection of high-risk patients may further reduce the incidence of fatal coronary events.

Multislice computed tomography coronary angiography (CTCA) enables the direct, noninvasive anatomic assessment of the coronary arteries, including the extent, severity and composition of plaques. Therefore, CTCA is more effective at detecting early-stage CAD than functional imaging techniques that assess myocardial perfusion and wall motion\(^{10}\). Identifying coronary plaques using CTCA has prognostic value; several studies have demonstrated that the extent of coronary plaques, as determined on CTCA, can predict all-cause mortality and the occurrence of major adverse cardiac events, including cardiac death, myocardial infarction and unstable angina pectoris requiring coronary revascularization\(^{11-16}\). These findings suggest that conducting risk assessments using CTCA are beneficial for improving the selection of patients who receive aggressive OMT, although it is important to carefully weigh the risk of contrast-induced nephropathy and radiation exposure. If the selection of patients for CTCA can be improved, then identifying coronary plaques using CTCA before the development of fatal CAD may allow for the more vigorous application of OMT and thereby reduce the risk of adverse cardiovascular events. However, the precise selection criteria for patients requiring CTCA remain unclear.

Adiponectin, a circulating protein derived from adipose tissue, protects vascular walls from atherosclerosis\(^{17}\). Studies of vascular injury models have shown that genetic ablation of adiponectin enhances vascular stenosis via neointimal thickening\(^{18}\) and that supplementation with adiponectin leads to a decrease in the concentration of lipid-rich plaques in the aortas of mice deficient in apolipoprotein E\(^{19}\). Furthermore, the circulating levels of adiponectin are decreased in patients with abdominal obesity and type 2 diabetes mellitus (DM)\(^{20, 21}\); this may partially explain why such patients are susceptible to atherosclerotic cardiovascular diseases.

Several studies have reported that, in humans, a low serum adiponectin level is associated with the presence of lipid-rich plaques and noncalcified plaques in coronary arteries assessed using intravascular ultrasound and CTCA, respectively\(^{22-25}\). These findings suggest the potential value of measuring the adiponectin level in order to select patients who require CTCA for further risk assessment. However, the clinical use of adiponectin as a biomarker in combination with conventional risk factors has not been fully evaluated. Therefore, in this study, we investigated significant risk factors associated with the extent of coronary plaques detected using CTCA and evaluated the usefulness of measuring the adiponectin concentration for identifying patients with a high risk of multivessel coronary atherosclerosis. Identifying significant risk factors for the development of multivessel coronary plaques, including the adiponectin level, should help to establish a noninvasive method for selecting patients who require CTCA in order to determine the appropriate treatment.

**Aim**

The aim of this study was to identify significant risk factors associated with the extent of coronary plaques detected using CTCA and to determine the value of measuring the adiponectin level for identifying patients at high risk of multivessel coronary atherosclerosis.

**Methods**

**Subjects**

We conducted a cross-sectional observational study of 298 consecutive patients with suspected CAD based on abnormal findings on electrocardiography and/or chest symptoms (such as chest pain, palpitations, dyspnea and/or chest discomfort) with at least one cardiac risk factor (DM, hypertension [HT], dyslipidemia and/or abdominal obesity). All patients underwent CTCA between July 2008 and October 2011 to detect CAD. Patients with extremely calcified coronary arteries that could not be assessed using CTCA and those treated with thiazolidinedione were excluded. Informed consent was obtained from all subjects, and the study protocol was approved by the Ethics Committee of Kure Medical Center.

**Laboratory Measurements**

Venous blood was drawn from all subjects after an overnight fast. The serum samples were either immediately analyzed or frozen at \(-80^\circ\text{C}\) for later measurement of the adiponectin concentration. The laboratory measurements included the serum concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and hemoglobin A1c (HbA1c). The concentrations of total cholesterol, triglycerides and HDL cholesterol were determined according to enzymatic methods using commercially available kits (Seikisui Medical Co., Tokyo). The level of HbA1c was estimated as the National Glycohemoglobin Standardization Program (NGSP)-equivalent percentage calculated using the following formula: \(\text{HbA1c (\%)} = 1.02 \times \text{NGSP-HbA1c - 0.03}\)
Assessment of Coronary Artery Atherosclerosis

We used a 64-slice multidetector-row computed tomography scanner (Somatom Definition AS; Siemens AG, Munich, Germany) with a workstation (Synapse Vincent; Fujifilm Co., Ltd, Tokyo, Japan) to reconstruct the CT images. CTCAs was performed using retrospective electrocardiography gating with the following parameters: rotation time, 300 ms/rotation; collimation, 128×0.6 mm; tube voltage, 120 kV; and tube current, 350 mAs. A bolus of 1 mL/kg of iopamidol (Iopamiron 370; Bayer, Japan) was injected intravenously followed by a 20-mL saline chaser. The images were initially reconstructed at the optimal phase of the cardiac cycle and assessed for coronary atherosclerosis. The extent of coronary artery atherosclerosis, defined as the number of coronary arteries with atherosclerotic plaque, either calcified or noncalcified, on the CTCAs images, was measured by two blinded cardiologists. Before the CTCAs examinations, a nonenhanced scan was performed to measure the coronary artery calcification score (CACS) and pericardial fat volume using a 120-kV tube voltage, 100-mA tube current and 2-mm section thickness. The CACS was calculated based on the Agatston score using a calcification threshold of >130 Hounsfield units (HU)\(^{27}\). Pericardial fat was defined as the presence of pixels within a window of -195 to -45 HU and was measured semi-automatically.

Definitions of DM, HT, Insufficient Control of LDL Cholesterol and Metabolic Syndrome

We used the Japanese criteria for classifying DM patients\(^{20}\). Similarly, we used the Japanese criteria for HT, which include elevated blood pressure (a systolic blood pressure [BP] of ≥140 mmHg and/or a diastolic BP of ≥90 mmHg) and/or the use of antihypertensive medications\(^{20}\). The patients were considered to have insufficient control of LDL cholesterol if they did not meet the target levels recommended by the Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases\(^{8}\). The patients were considered to have metabolic syndrome (MS) according to the Japanese criteria\(^{29}\), which require the presence of abdominal obesity and at least two of the following three factors: dyslipidemia (an elevated triglyceride level or a reduced HDL cholesterol level), elevated BP and elevated fasting glucose levels. More specifically, the components of MS were defined as follows: (1) a waist circumference of ≥85 cm for men and ≥90 cm for women; (2) an elevated serum triglyceride level of ≥150 mg/dL; (3) a reduced serum HDL cholesterol level of <40 mg/dL; (4) an elevated systolic BP of ≥130 mmHg and/or a diastolic blood pressure of ≥85 mmHg and/or the use of antihypertensive medications; and (5) an elevated fasting plasma glucose level of ≥110 mg/dL and/or the use of antidiabetic medications.

Statistical Analysis

Continuous variables were expressed as the mean and standard deviation (SD). Categorical and continuous variables were compared among the patients with three grades of coronary atherosclerosis using Pearson’s test and an analysis of variance (ANOVA), respectively. A logistic regression model was used to evaluate the associations between multivessel coronary atherosclerosis and the other variables. The odds ratios and 95% confidence intervals (CIs) were calculated. The predictive value of variables for assessing multivessel coronary atherosclerosis was evaluated using receiver operating characteristic (ROC) curves. The areas under the curve (AUCs), 95% CIs and probabilities were calculated. All statistical analyses were performed using the JMP version 9 (SAS Institute Japan Inc.) or SPSS Statistics version 19 (IBM SPSS Inc.) software programs. Statistical significance was defined as a p value of <0.05.

Results

Baseline Characteristics of the Subjects

This study comprised 298 patients (age, 67.7 ± 10.3 years; men, 58.7%). The clinical characteristics of the subjects are listed in Table 1. Of the patients, 29.9% had DM, 70.4% had HT, 35.6% had MS and 30.2% had insufficient control of LDL cholesterol. Most were receiving medications for these conditions, including statins, antihypertensive agents and antidiabetic agents. A total of 54.4% of the patients had chest pain, dyspnea or palpitations provoked by exertion and 23.5% had other symptoms, such as chest pain or discomfort, that lacked the characteristics of typical angina. The CTCA images indicated that 37.9% of the patients had normal coronary arteries,
26.8% had one diseased vessel, 20.1% had two diseased vessels and 15.1% had three diseased vessels.

**Associations between the Extent of Coronary Atherosclerosis and the Risk Factors**

The extent of coronary atherosclerosis was graded as normal, single-vessel or multivessel and was found to be significantly associated with age, sex, DM, HT, abdominal obesity, low HDL cholesterol and the serum levels of triglycerides, HDL cholesterol, HbA1c and adiponectin (Table 2).

**Relationships between Multivessel Coronary Atherosclerosis and the Risk Factors**

According to a univariate logistic regression analysis, the serum adiponectin concentration was found to be significantly associated with the presence of multivessel coronary atherosclerosis (Table 3). An advanced age (≥67 years, an optimal cutoff value according to the ROC curve analysis), male gender, DM, HT, a low HDL cholesterol level (<40 mg/dL), a high triglyceride level (≥150 mg/dL) and abdominal obesity were also significant risk factors related to multivessel coronary atherosclerosis (Table 3). Among these factors, a multivariate logistic regression analysis revealed that the serum adiponectin concentration was significantly associated with multivessel coronary atherosclerosis, independent of an advanced age, male gender, DM and HT (Table 3).

**Cumulative Effects of Age, Sex, a Low Adiponectin Level, DM and HT on Coronary Atherosclerosis**

In the current study, we defined a low serum adiponectin level (low-adipo) as a concentration of ≤10.8 μg/mL, an optimal cutoff value for multivessel coronary atherosclerosis according to the ROC curve analysis (AUC, 0.62) (Table 4). The ROC curve analysis revealed that the combination of five factors (age, sex, HT, DM and low-adipo) was a significant predictor of multivessel coronary atherosclerosis (AUC, 0.73; 95% CI, 0.67-0.78). The combination of five factors was a significantly better predictor than a combination of three factors (age, sex and HT; p=0.047) and better than a combination of four factors (age, sex, HT and DM; p=0.079), although not significantly. The predictive value of the five factors was not improved by adding three further conventional risk factors (low HDL cholesterol, high TG and abdominal obesity; p=0.632; Table 4). As the number of the five factors increased, the proportion of patients with multivessel coronary atherosclerosis increased, while the proportion of patients with normal coronary arteries decreased (Fig. 1).

**Table 1. Baseline characteristics of the subjects**

| N                  | 298 |
|--------------------|-----|
| Age (years), mean (SD) | 67.7 (10.3) |
| Sex (male), n (%), n (%) | 175 (58.7) |
| Risk factor diseases, n (%) | 106 (35.6) |
| diabetes mellitus | 89 (29.9) |
| hypertension | 210 (70.4) |
| metabolic syndrome | 89 (30.2) |
| insufficient control of LDL cholesterol | 210 (70.4) |
| Symptoms, n (%) | 90 (30.2) |
| any provoked by exertion | 162 (54.4) |
| others | 70 (23.5) |
| none | 66 (22.1) |
| Current medications, n (%) | 141 (47.3) |
| statins | 102 (34.2) |
| ACE-Is/ARBs | 109 (36.6) |
| calcium channel blockers | 55 (18.5) |
| β-blockers | 36 (12.1) |
| sulfonylureas | 32 (10.7) |
| metformin | 20 (6.7) |
| α-glucosidase inhibitors | 13 (4.4) |
| insulin injection | 88.1 (37.9) |
| CACS, median (min, max) | 113 (37.9) |
| pericardial fat volume, mean (SD) | 106.6 (42.7) |

**CTCA findings**

| number of diseased vessels, n (%) | 106.6 (42.7) |
|-----------------------------------|-------------|
| 0 | 113 (37.9) |
| 1 | 80 (26.8) |
| 2 | 60 (20.1) |
| 3 | 45 (15.1) |

**Cumulative Effects of Age, Sex, a Low Adiponectin Level, DM and HT on Coronary Atherosclerosis**

In the current study, we defined a low serum adiponectin level (low-adipo) as a concentration of ≤10.8 μg/mL, an optimal cutoff value for multivessel coronary atherosclerosis according to the ROC curve analysis (AUC, 0.62) (Table 4). The ROC curve analysis revealed that the combination of five factors (age, sex, HT, DM and low-adipo) was a significant predictor of multivessel coronary atherosclerosis (AUC, 0.73; 95% CI, 0.67-0.78). The combination of five factors was a significantly better predictor than a combination of three factors (age, sex and HT; p=0.047) and better than a combination of four factors (age, sex, HT and DM; p=0.079), although not significantly. The predictive value of the five factors was not improved by adding three further conventional risk factors (low HDL cholesterol, high TG and abdominal obesity; p=0.632; Table 4). As the number of the five factors increased, the proportion of patients with multivessel coronary atherosclerosis increased, while the proportion of patients with normal coronary arteries decreased (Fig. 1).

**Discussion**

The current study demonstrated that, among the various risk factors investigated, the circulating adiponectin level, age, sex, DM and HT are independently associated with the presence of multivessel coronary atherosclerosis detected on CTCA in patients with suspected CAD. Furthermore, the combination of these factors was found to be significantly associated with the extent of coronary atherosclerosis, and the number of these factors was found to be a significant predictor of multivessel coronary atherosclerosis.

CTCA allows for the noninvasive detection and characterization of coronary artery plaques, even when such lesions are not associated with significant luminal stenosis on angiography. Acute coronary syndrome (ACS) frequently results from lesions that were previ-
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These studies suggest that with suitable selection of patients, CTCA can be used to identify multiple coronary plaques before the development of fatal CAD, thus enabling the use of aggressive OMT and reducing the incidence of cardiovascular events. CTCA should not be performed in healthy subjects due to its radiation burden. Therefore, less invasive methods are required to identify high-risk patients who require CTCA. Our current findings indicate that, in addition to DM and HT, the adiponectin concentration is useful for predicting the coronary plaque burden, and its measurement is warranted for identifying individuals who would benefit from CTCA.

We and other researchers have shown that adiponectin exhibits antiatherogenic properties in both in...
patients who require CTCA for risk assessment and the subsequent application of aggressive OMT.

Although the adiponectin concentration has been reported to be predictive of the total coronary plaque burden\(^23\), our findings indicate that a low adiponectin level combined with the risk factors of age, sex, HT and DM is significantly better at predicting multivessel coronary atherosclerosis than the adiponectin level itself. The exact relationship between the adiponectin level and these other four factors in terms of the development of atherosclerosis remains to be determined. However, our findings are consistent with basic research indicating that adiponectin protects against direct proatherogenic stress on the vascular wall\(^18\). Compared with wild-type mice, adiponectin-null mice develop more severe atherosclerosis when the vascular wall is

### Table 4. Receiver operator characteristic curve analysis of the serum adiponectin levels and the number of risk factors required to predict multivessel coronary atherosclerosis

|                | Univariate | Multivariate |
|----------------|------------|--------------|
|                | OR (95% CI) | p value      | OR (95% CI) | p value      |
| Advanced age   | 2.2 (1.3-3.6) | 0.003        | 3.1 (1.7-5.6) | <0.001       |
| Male           | 2.2 (1.3-3.6) | 0.003        | 2.3 (1.3-4.2) | 0.006        |
| Diabetes mellitus | 2.1 (1.2-3.5) | 0.005        | 1.8 (1.0-3.2) | 0.038        |
| Hypertension   | 2.8 (1.5-4.9) | 0.001        | 2.3 (1.2-4.5) | 0.009        |
| Adiponectin (μg/dL) | 1.1 (1.0-1.1)* | 0.001        | 1.1 (1.0-1.1)* | 0.010        |
| Low HDL cholesterol | 3.6 (1.7-7.6) | 0.001        | 2.1 (0.9-5.0) | 0.088        |
| High triglyceride | 1.7 (1.0-2.9) | 0.038        | 1.3 (0.7-2.3) | 0.418        |
| Abdominal obesity | 1.9 (1.2-3.1) | 0.010        | 1.1 (0.6-1.9) | 0.847        |
| Metabolic syndrome | 1.6 (1.0-2.7) | 0.053        | –             | –            |
| Insufficient control of LDL cholesterol | 1.0 (0.6-1.6) | 0.851        | –             | –            |

The predictive factors were an advanced age (≥67 years), sex (male gender), diabetes mellitus (DM), hypertension (HT), a serum adiponectin concentration of ≤10.8 μg/mL; a low HDL cholesterol level, <40 mg/dL; a high triglyceride level, ≥150 mg/dL; abdominal obesity, a waist circumference of ≥85 cm (men) or ≥90 cm (women). A logistic regression model was used to evaluate the associations between multivessel coronary atherosclerosis and the other variables. *unit odds ratio; **range odds ratio.

### Table 3. Relationships between multivessel coronary atherosclerosis assessed using CTCA and various risk factors in the univariate and multivariate analyses

|                          | Univariate | Multivariate |
|--------------------------|------------|--------------|
|                          | OR (95% CI) | p value      | OR (95% CI) | p value      |
| Advanced age             | 2.2 (1.3-3.6) | 0.003        | 3.1 (1.7-5.6) | <0.001       |
| Male                     | 2.2 (1.3-3.6) | 0.003        | 2.3 (1.3-4.2) | 0.006        |
| Diabetes mellitus        | 2.1 (1.2-3.5) | 0.005        | 1.8 (1.0-3.2) | 0.038        |
| Hypertension             | 2.8 (1.5-4.9) | 0.001        | 2.3 (1.2-4.5) | 0.009        |
| Adiponectin (μg/dL)      | 1.1 (1.0-1.1)* | 0.001        | 1.1 (1.0-1.1)* | 0.010        |
| Low HDL cholesterol      | 3.6 (1.7-7.6) | 0.001        | 2.1 (0.9-5.0) | 0.088        |
| High triglyceride        | 1.7 (1.0-2.9) | 0.038        | 1.3 (0.7-2.3) | 0.418        |
| Abdominal obesity        | 1.9 (1.2-3.1) | 0.010        | 1.1 (0.6-1.9) | 0.847        |
| Metabolic syndrome       | 1.6 (1.0-2.7) | 0.053        | –             | –            |
| Insufficient control of LDL cholesterol | 1.0 (0.6-1.6) | 0.851        | –             | –            |

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; CI, confidence interval. The definitions of diabetes mellitus, hypertension, insufficient control of LDL cholesterol and metabolic syndrome are described in the Methods section. The other variables are defined as follows: an advanced age, ≥67 years; a low adiponectin level, ≤10.8 μg/mL; a low HDL cholesterol level, <40 mg/dL; a high triglyceride level, ≥150 mg/dL; abdominal obesity, a waist circumference of ≥85 cm (men) or ≥90 cm (women). A logistic regression model was used to evaluate the associations between multivessel coronary atherosclerosis and the other variables. *unit odds ratio; **range odds ratio.

**vitro and in vivo** experiments\(^18, 19\). Furthermore, low adiponectin levels are associated with the presence of CAD\(^36-38\). Recent clinical studies have shown that low adiponectin levels are associated with noncalcified and mixed plaques detected on CTCA\(^23-25\). However, the use of the adiponectin level as a biomarker for predicting the development of multiple coronary plaques in combination with conventional risk factors has not been fully evaluated. In the current study, a low serum adiponectin level was significantly associated with multivessel coronary atherosclerosis, independent of age, sex, DM and HT and was also predictive of the extent of coronary atherosclerosis when present in combination with the other four factors. Therefore, measuring the adiponectin level in addition to assessing these other factors is beneficial for selecting patients who require CTCA for risk assessment and the subsequent application of aggressive OMT.

Although the adiponectin concentration has been reported to be predictive of the total coronary plaque burden\(^23\), our findings indicate that a low adiponectin level combined with the risk factors of age, sex, HT and DM is significantly better at predicting multivessel coronary atherosclerosis than the adiponectin level itself. The exact relationship between the adiponectin level and these other four factors in terms of the development of atherosclerosis remains to be determined. However, our findings are consistent with basic research indicating that adiponectin protects against direct proatherogenic stress on the vascular wall\(^18\). Compared with wild-type mice, adiponectin-null mice develop more severe atherosclerosis when the vascular wall is
exposed to proatherogenic stressors (such as vascular injury), although they do not spontaneously develop atherosclerosis\(^{18}\). These data indicate that a low serum adiponectin concentration only reduces the mechanisms that protect vascular walls from these stressors and does not cause coronary atherosclerosis by itself. However, in the presence of proatherogenic stress, a reduced serum adiponectin concentration likely facilitates the development of atherosclerosis.

Our data suggest that, in addition to appropriate management of DM and HT to reduce proatherogenic stress, measures that improve the serum adiponectin level may be useful strategies for preventing the development of CAD. The adiponectin concentration has been shown to increase in response to diet-induced weight loss\(^{39, 40}\); however, few studies have reported the effects of dietary intervention on plasma adiponectin. Of the dietary fatty acids, n-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), increase the plasma adiponectin concentration. In obese humans with metabolic syndrome, the consumption of highly purified EPA increases the adiponectin concentration\(^{41}\). Although dietary supplementation with fish oil rich in EPA or DHA increases the adiponectin concentrations in rodents\(^{42}\), the same has not been conclusively demonstrated in humans. The production of adiponectin is induced by nuclear peroxisome proliferator-activated receptors gamma (PPAR-\(\gamma\))\(^{43}\), and thiazolidinediones and other pharmacological agents that activate PPAR-\(\gamma\) increase the adiponectin concentration\(^{44-46}\).

These agents, as well as diets high in n-3 PUFAs, are associated with a reduced risk of cardiovascular disease\(^{47-49}\), thus suggesting that a higher adiponectin concentration is important for preventing CAD.

All patients in this study were Japanese, and any differences with respect to other ethnic populations are unknown. This was a cross-sectional study conducted at a single medical center. In the future, conducting large-scale, prospective analyses at multiple centers is recommended in order to validate our findings. Our subjects were all consecutive patients who underwent CTCA in clinical practice to detect CAD, not asymptomatic patients who underwent CTCA for risk assessment, in accordance with the current guidelines for the use of CTCA. Therefore, we cannot draw definitive conclusions regarding the latter purpose. Our findings indicate that prospective clinical studies of asymptomatic high-risk patients or the general population are required to evaluate the efficacy of CTCA for risk assessment of the subsequent need for risk-reducing OMT.

**Conclusion**

The results of this study suggest that adiponectin is a useful biomarker for predicting the risk of multivessel coronary atherosclerosis detected on CTCA in combination with common risk factors (age, sex, DM and HT) in patients with suspected CAD. Based on these findings, we recommend that patients who test positive for more than three of the five factors undergo CTCA. The effective identification of patients with extensive coronary atherosclerosis and use of aggressive preventive measures should help to reduce future fatality rates associated with this disease.

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**Conflicts of Interest**

None to declare.

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