

Noninvasive Assessment of Gender Differences in Coronary Plaque Composition with Multidetector Computed Tomographic Angiography

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To date, sparse data are available with regard to gender differences in plaque morphology and composition. The aim of the present report was to assess the differences in coronary plaque burden and composition in a noninvasive manner between women and men using multidetector computed tomographic angiography. The study population consisted of 416 patients (61 ± 13 years), with 148 women (36%). A stenosis of $\geq 70\%$ in at least one coronary segment was found in 11% of women compared to 25% of men ($p < 0.0001$). Overall, women presented with a significantly lower mean number of segments containing calcified plaques (1.43 ± 2.04 vs 2.25 ± 2.30 , $p = 0.004$) and mixed plaques (1.67 ± 1.23 vs 2.25 ± 2.30 , $p = 0.05$). No such relation was seen with noncalcified plaques (0.72 ± 1.01 vs 0.86 ± 1.06 , $p = 0.21$). In addition, the assessment of the overall proportion of the composition of plaque burden revealed relatively more noncalcified (40% vs 28%), less calcified (38% vs 43%), and mixed (23% vs 28%) plaques in women than in men ($p < 0.0001$). On multivariate analysis of the total plaque burden, the women had a 19% (95% confidence interval 11% to 28%, $p < 0.0001$) greater relative distribution of plaque that was noncalcified compared to the men, and the overall plaque burden was less likely to be calcified ($p = 0.006$) or mixed ($p = 0.019$). Similar results were seen in younger and older subjects. In conclusion, gender differences exist, not only in the atherosclerotic disease burden, but also in the underlying plaque composition. Women tended to have more exclusively noncalcified plaque and were less likely to have calcified or mixed plaques compared to men. Future studies are needed to elucidate whether these underlying differences in plaque composition might explain the reduced risk of cardiac events in women. © 2010 Elsevier Inc. All rights reserved. (Am J Cardiol 2010;105:453–458)

The advent of multidetector computed tomographic angiography (MDCTA) has provided the ability to obtain comprehensive information regarding the location, severity, and characteristics of coronary atherosclerotic plaques, such as noncalcified, calcified, and mixed plaques.^{1–3} Coronary atherosclerotic plaque composition, rather than the plaque size or the degree of coronary artery stenosis, has been shown to be an important determinant of the evolution and disruption of the plaque.^{4,5} The greater coronary artery disease (CAD) event rates in men compared to women

could be a result of the differences in coronary plaque burden^{6–9} and composition.^{10,11} Therefore, understanding the gender differences in plaque characteristics might be vital in understanding the gender-related differences in CAD. Thus, the purpose of the present study was to evaluate whether gender differences in the extent and composition of coronary plaques could be observed using coronary MDCTA.

Methods

We evaluated 416 consecutive, symptomatic patients with an intermediate to high risk of CAD who had been referred for MDCTA. The institutional review board committee board of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Torrance, California) approved the study protocol and consent form. MDCTA was requested for indications that included chest pain, shortness of breath, abnormal or equivocal stress test findings, cardiomyopathy, congestive heart failure, and syncope. Most patients presented for an evaluation of chest pain (346 of 416 [83%]). No gender differences were seen in the indication for MDCTA. In addition, none of the patients had had previous myocardial infarction or known CAD. The baseline demographic data, a history of hypertension, hy-

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Table 1
Characteristics of study population according to gender

Characteristic	Women (n = 148)	Men (n = 268)	p Value
Age (years)	62 ± 13	60 ± 13	0.18
Diabetes mellitus	19%	12%	0.04
Hypertension*	47%	39%	0.11
Hypercholesterolemia [†]	55%	55%	0.97
Smoker	5%	6%	0.70
Family history of premature coronary artery disease	56%	45%	0.03
Body mass index (kg/m ²)	28 ± 6	28 ± 5	0.90
Lipid-lowering medication	17%	16%	0.82

* Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or blood pressure-lowering medication.

[†] Defined as elevated total cholesterol, low-density lipoprotein, or triglycerides and/or low high-density lipoprotein.

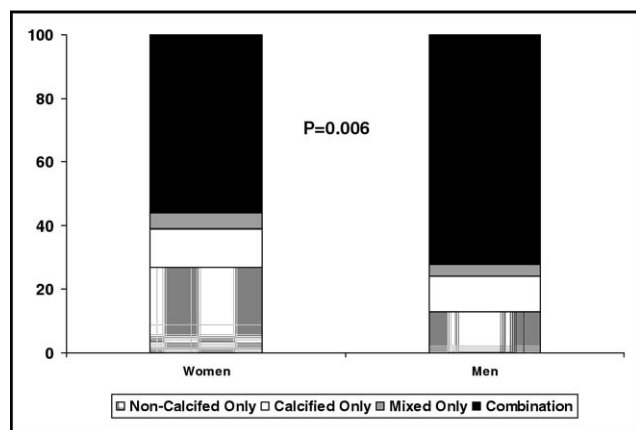


Figure 1. Frequency of women and men with plaque subtypes in presence of CAD.

Table 2
Characteristics of stenotic coronary artery disease according to gender

Characteristic	Women (n = 148)	Men (n = 268)	p Value
Narrowing >70% in diameter	17 (12%)	66 (25%)	<0.0001
Maximal diameter stenosis			<0.0001
No plaque	34 (23%)	17 (6%)	
1-49%	81 (54%)	156 (58%)	
50-70%	16 (11%)	29 (11%)	
>70%	17 (12%)	66 (25%)	
Narrowed coronary arteries			<0.0001
0	131 (88%)	202 (75%)	
1	10 (6%)	45 (17%)	
2	6 (4%)	15 (6%)	
3	1 (1%)	6 (2%)	

perlipidemia, and diabetes mellitus, smoking, and a family history of CAD were collected for all patients.

All multidetector computed tomographic angiographic scans were performed with a 64-detector row Lightspeed VCT scanner (GE Healthcare, Milwaukee, Wisconsin). All patients were in normal sinus rhythm at MDCTA. The patients presenting with a baseline heart rate >65 beats/min were administered oral β -blocker therapy as the preferred method for slowing the heart rate. When necessary, intra-

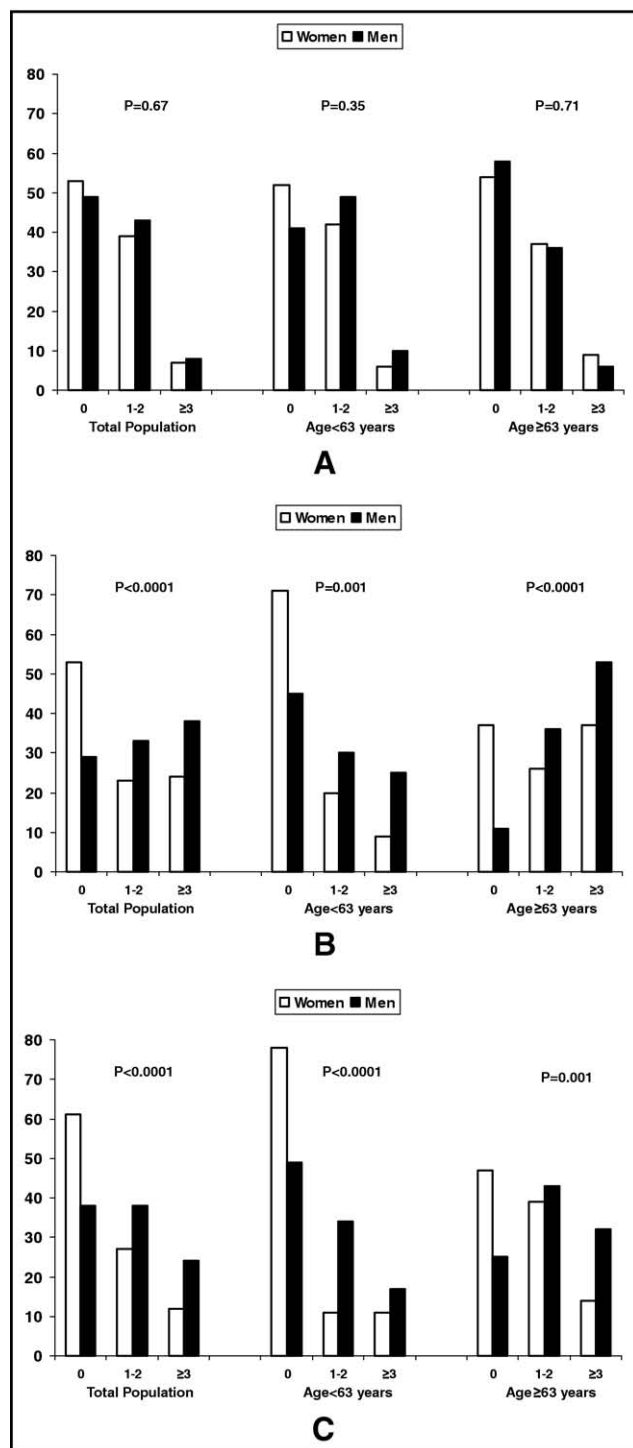


Figure 2. Frequency (%) of coronary segments with (A) noncalcified plaque, (B) calcified plaque, and (C) mixed plaque according to gender.

venous metoprolol was administered to a total possible dose of 40 mg to achieve a heart rate at rest of <65 beats/min. All patients eligible for MDCTA underwent scanning, irrespective of whether the heart rate goal of <65 beats/min had been achieved. After a scout X-ray of the chest (anteroposterior and lateral), a timing bolus (using 10 to 20 ml of contrast) was performed to detect the interval to optimal contrast opacification in the axial image at a level immedi-

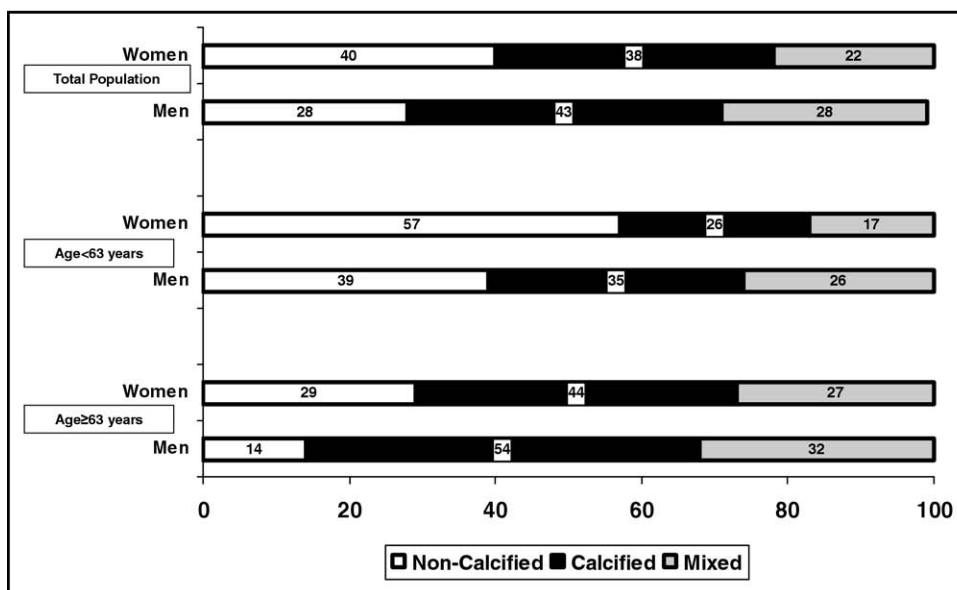


Figure 3. Relative distribution (%) of coronary segments with plaque types according to gender.

ately superior to the ostium of the left main artery. Nitroglycerin 0.4 mg sublingually was administered immediately before contrast injection. During MDCTA, 80 ml iodinated contrast was injected using a triple phase contrast protocol (60 ml iodixanol, followed by 40 ml of a 50:50 mixture of iodixanol and saline, followed by a 50-ml saline flush). Retrospective electrocardiographic gated helical contrast-enhanced MDCTA was performed, with scan initiation 20 mm above the level of the left main artery to 20 mm below the inferior myocardial apex. The scan parameters were 64×0.625 mm collimation, tube voltage 120 kV, effective mA 350 to 780 mA. Radiation-reduction algorithms using electrocardiographic modulation were used to reduce the radiation exposure (mA) during systole and end-diastole. After scan completion, multiphase reconstruction of the multidetector computed tomographic angiographic scans was performed, with reconstructed images from 70% to 80% by 5% and 5% to 95% by 10% increments. The multidetector computed tomographic angiographic images were reviewed by 2 experienced observers who were unaware of the patients' clinical history. A high degree of agreement was observed (98%); in the case of disagreement, a final verdict was reached by consensus with a third experienced reader. All images were evaluated on a 3-dimensional image analysis workstation (GE Advantage Workstation, GE Healthcare). The coronary arteries were scored using a 15-segment American Heart Association coronary artery classification, as previously described.¹² An overall assessment of image quality and coronary supply dominance was performed on the subject level. For each coronary segment, the readers assessed whether the coronary segments were evaluable. The segments were evaluated for the presence or absence of coronary plaques using axial images and curved multiplanar reconstruction. One coronary plaque type was assigned per segment. The plaques were defined as structures $>1 \text{ mm}^2$ within and/or adjacent to the vessel lumen that could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques occu-

ried by calcified tissue for $>50\%$ of the plaque area (density >130 Hounsfield units on native scans) were classified as calcified, plaques with $<50\%$ calcium were mixed, and plaques without any calcium were classified as noncalcified lesions. The calcified area was assessed manually.

To assess the independent relation of the different plaque subtypes with the degree of coronary stenosis, we performed linear regression analysis (with the total number of segments involved with plaque subtypes as the dependent variable) and logistic regression analysis (≥ 3 segments involved with plaque subtypes as the dependent variable). As a first step, we performed univariate analysis, followed by multivariate analysis, taking into account age, hypertension, diabetes mellitus, smoking, family history of coronary heart disease, hypercholesterolemia, body mass index, and lipid-lowering medications. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata, version 8.0 (StataCorp, Austin, Texas). The investigators had full access to the data and take full responsibility for its integrity. All investigators have read and agreed to the report as written.

The study population consisted of 416 symptomatic (mean age 61 ± 13 years, 36% women) patients who had undergone coronary MDCTA for assessment of underlying CAD. Table 1 lists the study population characteristics according to gender. Women were more likely than men to report diabetes mellitus and a family history of CAD ($p < 0.05$). However, no statistically significant differences between the men and women were observed in age, prevalence of hypertension, hypercholesterolemia, cigarette smoking, or obesity (Table 1).

In our study participants, CAD was completely absent on coronary MDCTA in 51 (12%); a feature more likely in women than in men (23% vs 6%, $p < 0.0001$). In the remaining 365 patients (88%) with underlying CAD, 63 (17%) had exclusively noncalcified plaques, 42 (11%) had exclusively calcified plaque, and 16 (4%) had mixed plaque. Most patients had a combination of the 3 plaque subtypes

Table 3
Multivariate regression analysis demonstrating association between women vs men and extent of coronary atherosclerotic plaque (noncalcified, mixed, and calcified)

Increasing No. of Segments With Plaque	β (95% CI)		p Value
	Men (n = 268)	Women (n = 148)	
Noncalcified			
Model 1	0 (Referent)	-0.12 (-0.33 to 0.09)	0.26
Model 2	0 (Referent)	-0.15 (-0.37 to 0.06)	0.17
Calcified			
Model 1	0 (Referent)	-0.92 (-1.34 to -0.51)	<0.0001
Model 2	0 (Referent)	-1.04 (-1.48 to -0.62)	<0.0001
Mixed			
Model 1	0 (Referent)	-0.72 (-1.04 to -0.39)	<0.0001
Model 2	0 (Referent)	-0.79 (-1.12 to -0.44)	<0.0001

Model 1 adjusted for age.

Model 2 adjusted for age, hypertension, diabetes mellitus, smoking, family history of CAD, hypercholesterolemia, and body mass index.

CI = confidence interval; β = β estimate, predicted increase in mean number of coronary segments with plaque subtypes (women vs men).

Table 4
Odds ratio (95% confidence interval) for presence of ≥ 3 segments with plaque (women vs men) on multivariate-adjusted analysis

≥ 3 Segments With Plaque	Odds Ratio (95% CI)		p Value
	Men (n = 268)	Women (n = 148)	
Noncalcified			
Model 1	1 (Referent)	0.96 (0.45–2.05)	0.91
Model 2	1 (Referent)	0.86 (0.08–1.71)	0.21
Calcified			
Model 1	1 (Referent)	0.45 (0.28–0.72)	0.001
Model 2	1 (Referent)	0.38 (0.23–0.63)	<0.0001
Mixed			
Model 1	1 (Referent)	0.40 (0.22–0.71)	0.002
Model 2	1 (Referent)	0.35 (0.19–0.64)	0.001

Model 1 adjusted for age.

Model 2 adjusted for age, hypertension, diabetes mellitus, smoking, family history of coronary heart disease, hypercholesterolemia, body mass index, and lipid-lowering medication.

Abbreviation as in Table 3.

(n = 244, 67%). As shown in Figure 1, women were more likely to have exclusively noncalcified plaque (27% vs 13%) and less likely to have a combination of plaque subtypes (56% vs 72%). As listed in Table 2, women were less likely to have at least one coronary segment with a luminal diameter stenosis of $\geq 70\%$ (12% vs 25%, p < 0.0001) and were less likely to have significant stenosis involving 2 to 3 vessels.

Overall, women presented with a significantly lower mean number of segments containing calcified plaques (p = 0.004) and mixed plaques (p = 0.05). However, no such relation was seen with noncalcified plaques (p = 0.21). As shown in Figure 2, no difference in the distribution of coronary segments (0, 1 to 2, ≥ 3) with noncalcified was observed between the genders, with similar results when stratified according to median age (<63 and ≥ 63 years).

Table 5
Multivariate regression analysis demonstrating association between women vs men and relative distribution (%) of coronary atherosclerotic plaque (noncalcified, mixed, and calcified)

Relative Distribution	β (95% CI)		p Value
	Men (n = 268)	Women (n = 148)	
Noncalcified			
Model 1	0 (Referent)	17% (9% to 25%)	<0.0001
Model 2	0 (Referent)	19% (11% to 28%)	<0.0001
Calcified			
Model 1	0 (Referent)	-9% (-16% to -1%)	0.03
Model 2	0 (Referent)	-11% (-19% to -3%)	0.006
Mixed			
Model 1	0 (Referent)	-8% (-14% to -1%)	0.017
Model 2	0 (Referent)	-8% (-14% to -1%)	0.019

Model 1 adjusted for age.

Model 2 adjusted for age, hypertension, diabetes mellitus, smoking, family history of coronary heart disease, hypercholesterolemia, and body mass index.

Abbreviation as in Table 3.

Examination of the distribution of calcified and mixed plaques (Figure 2) revealed that the proportion of women with ≥ 3 segments was much lower than that of men (p < 0.0001). Although we observed no differences in the total number of coronary segments with noncalcified plaque according to gender, the relative distribution of plaque types was significantly more likely to be noncalcified and less likely to be calcified and mixed in women. These differences persisted when stratified according to the median age of the study population (Figure 3).

On multivariate adjusted analyses (Table 3), after taking into account age and coronary heart disease risk factors, women were less likely than men to have an increased number of coronary segments with calcified and mixed plaque, with no significant differences observed in the number of segments with noncalcified plaque. The odds ratio for a high calcified and mixed plaque atherosclerotic burden (≥ 3 segments) in women compared to men was 0.38 (95% confidence interval 0.23 to 0.63) and 0.35 (95% confidence interval 0.19 to 0.64), respectively (Table 4). In addition, women had a 19% (p < 0.0001) greater relative distribution of plaque that was noncalcified and the relative plaque burden was less likely to be calcified (p = 0.006) or mixed (p = 0.019) than in men (Table 5).

Discussion

The present study represents the first comprehensive assessment of gender differences in plaque composition using coronary MDCTA. Our study findings are consistent with previous reports that women overall have less plaque burden and extend previous observations by demonstrating that in the presence of CAD, women have relatively more noncalcified plaques and less calcified and mixed plaques than men. This relation appeared to be independent of age and coronary heart disease risk factors.

To date, few studies have investigated the gender differences in coronary plaque composition and morphology.

Mautner et al,¹³ in an autopsy study of patients who had died after coronary artery bypass surgery, assessed nearly 1,000 5-mm segments of native coronary arteries. Their findings revealed that atherosclerotic plaques in women compared to men contained significantly more cellular fibrous tissue in the native coronary arteries (mean 38% vs 4%, $p < 0.001$). In addition, Dollar et al¹⁴ also demonstrated that, on autopsy, significantly more cellular fibrous tissue and lipid-rich foam cells and lesser amounts of dense fibrous and heavily calcified tissue was seen in epicardial arteries. Rasheed et al¹⁰ performed intravascular ultrasound measurements in 146 patients (29% women) and reported that 67% of plaques in women and 53% of plaques in men were considered soft. Subsequently, Sheifer et al¹¹ assessed the relative density of plaque quantitatively by videodensitometry using intravascular ultrasonography of coronary plaques in 106 patients (28% women) with unstable angina pectoris. They reported that the coronary plaques were less dense ($74 \pm 23\%$ vs $86\% \pm 22\%$ of adventitial density, $p = 0.02$) and were less often calcified (20% vs 38%, $p = 0.05$).⁵ However, intravascular ultrasound studies have been limited to a few segments and were not able to take into account the overall plaque characteristics.

Our study has extended the findings of existing evidence by demonstrating, for the first time, that women have a lower calcified and mixed plaque burden, with no differences found in noncalcified plaque compared to men. These differences persisted in all age groups. In addition, despite the similar overall noncalcified plaque burden, women had a greater proportion of noncalcified to total plaque (ie, larger relative burden of noncalcified plaque). The potential mechanisms of the presence of a greater proportion of noncalcified plaque in women are not entirely clear, and additional research is needed to determine whether factors related to endogenous hormonal factors, such as estrogen, might play a role. For instance, estrogen is known to influence underlying lipid metabolism and endothelial function and, thus, might influence the development and maturation of plaque. Furthermore, intravascular ultrasound and autopsy data have suggested that sex hormones might mediate atherosclerotic plaque expansion in women.^{15–17}

In recent years, the development of contrast-enhanced coronary computed tomography has enabled the identification of soft plaques (exclusively calcified or mixed plaque) and has generated great enthusiasm, given the potential for identifying “vulnerable plaques.” Currently, it is not entirely clear whether both or one of these plaque subtypes predispose patients to greater cardiovascular risk; however, emerging data suggest that a mixed plaque burden is more likely to be associated with an elevated risk of adverse outcomes. In a landmark study, Lin et al¹⁸ reported that mixed plaques were more likely to be associated with an increased likelihood of myocardial perfusion abnormalities. In contrast, calcified and noncalcified plaque scores did not predict ischemia. Recently, Pundziute et al¹⁹ assessed the presence of thin-cap fibroatheromas (a known marker of plaque vulnerability) by virtual histologic intravascular ultrasonography according to plaque subtype observed on 64-slice computed tomographic angiography. In their study, thin-cap fibroatheromas were most frequently observed in

mixed plaques compared to noncalcified and calcified plaques (32%, 13%, and 8%, respectively; $p = 0.002$).¹⁹ In addition Pundziute et al,²⁰ in a follow-up study of a small sample size of 100 patients, provided data that a mixed plaque burden is a significant predictor of adverse events. The observation in our study that men, who are more likely to experience an acute cardiovascular event, had a greater proportion and burden of mixed plaques compared to women, has strengthened the notion that mixed plaques might be more likely to be associated with an increased risk of cardiovascular events. Although MDCTA provides an excellent opportunity to identify the natural history of plaque development and progression and might aid in improving our understanding of underlying coronary plaque composition according to varying risk profiles, well-designed, prospective studies are needed to establish the predictive value of each specific plaque subtype, especially whether MDCTA can further refine risk stratification beyond the determination of global plaque burden.

Our study had several limitations. Our cohort was composed of symptomatic patients; thus, the results might not be generalizable to asymptomatic subjects. In addition, most patients in our study were whites; however, assessing the differences across different racial groups is of utmost importance.²¹ Finally, we did not have data on the outcomes related to plaque composition to determine which plaque subtypes might be more predictive of events in a specific gender.

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