Prevalence of coronary artery disease in low to moderate-risk asymptomatic women: a multislice computed tomography study

Düşük ve orta riskli asemptomatik kadınlarda koroner arter hastalığı prevalansının çokkesitli bilgisayarlı tomografi ile değerlendirilmesi

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Objectives: Traditional risk factors may underestimate the burden of subclinical atherosclerosis in women. Recently, multislice computed tomography (MSCT) has become widely available in detecting early coronary artery disease (CAD). We sought the prevalence of CAD in low to moderate-risk asymptomatic women by MSCT coronary artery calcium (CAC) scoring and coronary angiography.

Study design: The study included 185 women (mean age 57±12 years) without known CAD and diabetes, with low or moderate risk for CAD based on traditional risk scoring. Coronary artery calcium scoring and coronary angiography were performed by MSCT, which included a segment-based plaque detection and characterization of calcification. The plaques were classified based on the luminal stenotic effect (>50%). Patients with ≥1 stenotic plaque were classified as having obstructive CAD. Angiographic findings were compared with calcium scores.

Results: Coronary artery calcium scoring and coronary angiography detected CAD in 63 (34.1%) and 100 (54.1%) women, respectively. In both groups, women were significantly older and had higher prevalences of hypertension and dyslipidemia. Coronary angiography showed CAD in 41 women (41%; 14.6% were obstructive) without CAC. These women were significantly younger than those with a positive CAC score (p<0.01). Age (p<0.02) and hypertension (p<0.05) were found as independent predictors of CAD detected by coronary angiography.

Conclusion: Multislice computed tomography identified a subset of low-risk women who might be at higher risk than that suggested by current risk stratification strategies. Women, especially having hypertension and dyslipidemia may be potential candidates for further risk stratification by MSCT coronary angiography.

Key words: Atherosclerosis; calcinosis/radiography; coronary angiography; coronary artery disease; coronary stenosis; female; risk assessment; tomography, X-ray computed/methods.

Amaç: Geleneksel risk faktörleri kadınlarda erken aterosklerozun değerlendirilmesinde yetersiz kalabilmektedir. Çokkesitli bilgisayarlı tomografi (ÇKBT) koroner arter hastalığının (KAH) erken tanısında yaygın olarak kullanılmaya başlamıştır. Bu çalışmada, ÇKBT koroner arter kalsiyum (KAK) skorlaması ve koroner anjiyografi ile düşük ve orta riskli asemptomatik kadınlarda KAH prevalansı araştırıldı.

Çalışma planı: Çalışmaya, bilinen KAH ve diyabeti olmayan, geleneksel risk skorlamasına göre düşük-orta riskli 185 kadın alındı (ort. yaş 57±12). Çokkesitli bilgisayarlı tomografi ile KAK skorlama ve koroner anjiyografi yapıldı. Plak değerlendirmesi segmenter düzeyde yapıldı ve plaklar kalsifikasyon yönünden ve lümendeki darlık etkisine (>%50) göre sınıflandırıldı. Bir veya daha fazla >%50 plağı olan hastalar tıkayıcı KAH grubunda kabul edildi. Koroner anjiyografi ve KAK skorlama sonuçları karşılaştırıldı.

Bulgular: Koroner arter kalsiyum skorlama ile 63 olguda (%34.1), koroner anjiyografi ile 100 olguda (%54.1) KAH saptandı. İki grupta da olgular normal gruba göre daha ileri yaşta idi ve hipertansiyon ve dislipidemi sıklığı anlamlı derecede daha fazlaydı. Koroner anjiyografi ile ateroskleroz saptanan olguların 41'inde (%41) KAK skoru 0 idi ve bunların %14.6'sında tıkayıcı KAH vardı. Bu olgular, KAK skoru pozitif olan gruba göre daha gençti (p<0.01). Yaş (p<0.02) ve hipertansiyon (p<0.05) koroner anjiyografi ile saptanan KAH'nin bağımsız belirteçleri olarak bulundu.

Sonuç: Konvansiyonel yöntemle düşük-orta riskli sayılabilecek bir grup kadının aslında KAH açısından daha yüksek riskli olduğu ÇKBT koroner anjiyografi ile belirlenmiştir. Kadınlarda, özellikle hipertansiyon ve dislipidemi varlığında risk sınıflamasında ÇKBT koroner anjiyografi uygun bir yöntem olarak kullanılabilir.

Anahtar sözcükler: Ateroskleroz; kalsiyum/radyografi; koroner anjiyografi; koroner arter hastalığı; koroner darlık; kadın; risk değerlendirmesi; bilgisayarlı tomografi/yöntem.

Received: May 27, 2008 *Accepted:* August 13, 2008

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Cardiovascular disease (CVD) is the leading cause of mortality in women in the developed countries and coronary artery disease (CAD) accounts for nearly half of all CVD deaths.[1] Currently, estimation of risk in primary prevention is based on the Framingham risk equations, which input traditional risk factors and are helpful in predicting the development of CHD. Although traditional risk factors are very helpful in predicting the development of CAD in women, many women suffer events in the absence of established risk factors for atherosclerosis and broad-based population risk estimations may have little precision when applied to a given individual. Therefore, further work is needed to understand if certain groups of women, despite a low-risk designation based on traditional risk factors, might actually be at greater risk for CAD and potentially merit more aggressive preventive medical therapy. To date, several tools have been developed to identify atherosclerotic disease at its preclinical stages, with the hope of modifying its natural history and progression.

The goal of this study was to determine the prevalence of subclinical CAD with coronary artery calcium (CAC) scoring and coronary angiography using multislice computed tomography (MSCT) among asymptomatic women who were classified as being at low and/or intermediate risk based on traditional risk scoring.

PATIENTS AND METHODS

Study population. This is a cross-sectional study on a consecutive sample of 1,000 physician- or self-referred individuals who presented to a single MSCT scanning facility between August 2006 and April 2007 for CAD risk stratification. Female subjects were chosen for the study and assessed for eligibility. The exclusion criteria were known CAD and any current symptoms potentially suggestive of angina (asymptomatic status was confirmed by WHO questionnaire for each patient).[2] Since the Framingham risk equation from Adult Treatment Panel (ATP) III counts diabetics as a CHD-risk equivalent,[3] patients with diabetes mellitus were also excluded. Diabetes mellitus was defined as current use of antidiabetic medication or known but untreated diabetes. Finally, patients with ventricular and/or supraventricular arrhythmias and contraindications for the use of iodinated contrast media were excluded.

Risk factor assessment. All individuals provided details of their demographics, medical history, and current medications. The following conditions were questioned for each individual: arterial hypertension (defined as current use of antihypertensive medication or presence of untreated high blood pressure above 140/90 mmHg), hypercholesterolemia (defined as current use of antilipid therapy or known but untreated hypercholesterolemia), current smoking (including cessation of smoking within the past three months) or family history of premature CAD (defined as the occurrence of CAD in a first-degree relative before the age of 55 years for males or 60 years for females). Body mass index (BMI) was calculated from self-reported height and weight and BMI >30 kg/m^2 was considered to show obesity.

The study sample consisted of 185 asymptomatic women without known CAD and diabetes and having ≤2 of the above-described risk factors which corresponded to a low or intermediate risk profile for CHD based on the traditional risk assessment. All patients gave written informed consent and the study was approved by the local ethical committee.

MSCT scan protocol and data acquisition. Imaging was performed using a 64-slice MSCT scanner (Philips Brilliance, Philips Medical Systems, Eindhoven, Netherlands), with a pitch of 0.2, a tube voltage of 120 kV, and a tube current of 600-800 mAs. Pharmacologic premedication with beta-blockers for optimization of the heart rate was applied as previously described by our group.[4] The electrocardiogram was digitally recorded during data acquisition and was stored with the unprocessed MSCT data set. First, a prospectively gated coronary calcium scan was performed before MSCT angiography. Accordingly, data were acquired with a collimation of 64 x 0.5 mm and a tube rotation time of 400 msec, and a tube current of 300 mA at 120 kV for patients with normal posture. In case of patients with a higher body mass index (>30 kg/m^2), the tube current was increased to 350-500 mA at 135 kV. Depending on the total scan time, 80-110 ml nonionic contrast material (Iomeron 400, Bracco s.p.a., Milan, Italy) was administered in the antecubital vein with a flow rate of 5.0 ml/sec, followed by a 50-ml saline bolus. Automated peak enhancement detection in the descending aorta was used for timing of the bolus using a threshold of +130 Hounsfield units. Data acquisition was performed during an inspiratory breath hold of approximately 10 seconds. All data sets were reconstructed using retrospective gating in 45%, 80% and (as default) 75% of the RR interval, with a slice thickness of 0.9 mm. The reconstructed image data of the CT were transferred to a stand-alone workstation for postprocessing (EBW; Philips Medical Systems).

Coronary calcium scoring. Coronary artery calcium was quantified using the scoring method described by Agatston et al.[5] Calcium was considered present in a coronary artery when a density of >130 Hounsfield units was detected in more than three contiguous pixels (>1 mm^2) overlying that coronary artery. The CAC score was computed from the product of the attenuation factor and the area of calcification (mm^2). The total CAC score of each coronary artery was derived from the sum CAC score of all the lesions from that artery. The overall total CAC score was calculated by summing CAC scores from the left main, left anterior descending, left circumflex, and right coronary arteries. Age- and gender-matched percentiles were determined based on previously described values in the population.[6] Coronary artery calcium corresponding to the ≥75th percentile matched for age- and gender-based data was considered 'significant CAC'.

MSCT angiographic data analysis. All coronary angiograms were analyzed by an experienced radiologist and a cardiologist who were blinded to the clinical history and CAC score of the patients. In case of disagreement, another experienced reader reviewed the angiograms and a consensus decision was made. Image quality was evaluated on a per-segment basis and classified as good (defined as the absence of any image-degrading artifacts related to motion, calcification, or noise), adequate (despite the presence of image-degrading artifacts, evaluation is possible with moderate confidence), or poor (image-degrading artifacts enables no evaluation or only limited evaluation with low confidence). The angiograms were evaluated according to the modified classification of the American College of Cardiology/American Heart Association (ACC/AHA).[7]

Plaque detection and evaluation. The presence of atherosclerotic plaque was reported when there was a CT structure >1 mm^2 within and/or adjacent to the coronary artery lumen that could be distinguished from both the vessel lumen and the surrounding pericardial tissue using both cross-sectional and curved multiplanar reconstructed images as described by Leber et al.[8]

All available coronary segments were visually assessed for the degree of stenosis. The lesions were divided in two groups based on the severity of luminal stenotic effect. Lesions that caused a luminal narrowing of less than 50% were defined as nonstenotic and a narrowing of ≥50% were defined as stenotic plaque. Patients with no plaque were considered to be normal, whereas those with ≥1 nonstenotic plaque and ≥1 stenotic plaque were considered to have nonobstructive and obstructive CAD, respectively.

Coronary artery plaques were reported as soft, mixed, or calcified according to their CT densities. Plaques with a lower density compared to the contrast enhanced vessel lumen were defined as soft, while plaques with a higher density were defined as calcified. Mixed plaque was defined as a single plaque that contained both soft and calcified components.

Statistical analysis. Continuous variables were expressed as mean and standard deviation. Frequencies were expressed in percentages. Statistical analysis was performed using SPSS for Windows (version 10). The distribution of values was assessed by the Kolmogorow-Smirnow test for homogeneity of variances. Distribution of CAC scores and coronary artery plaques in various risk groups was tested by Kruskall-Wallis test and Mann-Whitney U-test. Chi-square test was used to test for differences between dichotomous variable groups. Independent predictors of CAD were sought by multivariate linear regression analysis.

RESULTS

The final study sample consisted of 185 asymptomatic nondiabetic women (mean age 57±12 years). Baseline characteristics of the study population are outlined in Table 1.

Coronary calcium scoring. The number of women with detectable CAC was 63 (34.1%). The mean CAC

Table 1. The demographics and baseline characteristics of the study group

	Coronary artery calcium						
	Absent (n=122)			Present (n=63)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			54±12			65±11	0.0001
Body mass index (kg/m^2)			22±5			27±6	0.001
Hypertension	64	52.5		48	76.2		0.002
Dyslipidemia	39	32.0		31	49.2		0.02
Smoking	34	27.9		16	25.4		0.6
Family history	57	46.7		31	49.2		0.7

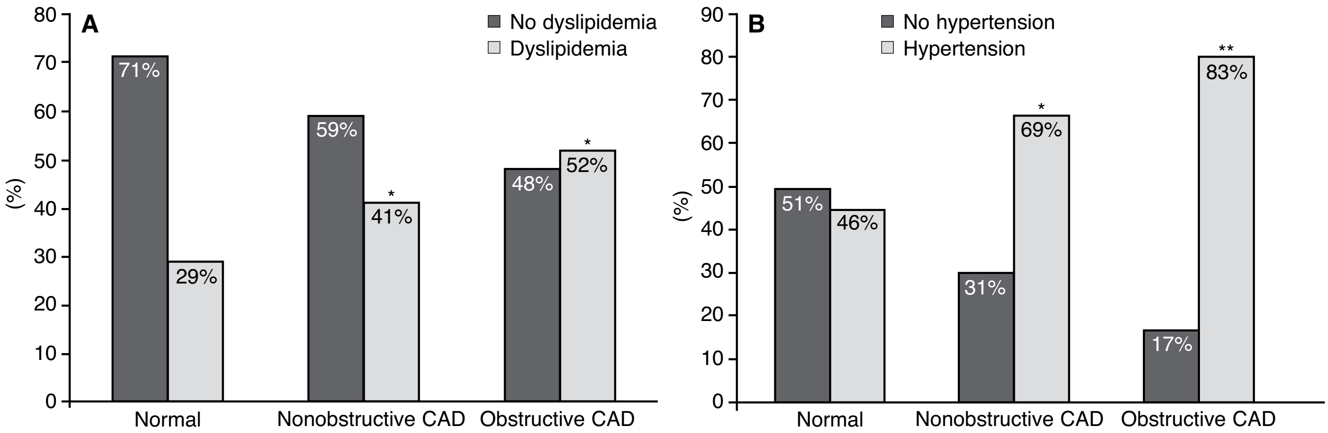

Figure 1. The frequencies of **(A)** dyslipidemia and **(B)** hypertension in women with no coronary artery disease (CAD), nonobstructive CAD, and obstructive CAD detected by multislice computed tomography coronary angiography. The prevalences of dyslipidemia and hypertension were higher in nonobstructive and obstructive CAD groups compared to normals. Additionally, the prevalence of hypertension increased significantly with the degree of CAD and was the highest in obstructive CAD. *p<0.05 *vs* normals; **p<0.05 *vs* normals and nonobstructive CAD.

score was 98±289 (range 0 to 2556). Overall, 8.7% of the women (n=16) had age- and gender-derived 25th percentile, 13% (n=24) had 25-75th percentile, 8.7% (n=16) had 75th percentile, and 3.8% (n=7) had 90th percentile of the CAC score. It is important to note that ≥75th percentile, which corresponded to 13% of the study population, is an established marker for future CHD events.[9] Asymptomatic individuals with detectable CAC were significantly older (65±11 years *vs* 54±12 years, p<0.0001) and had higher prevalences of arterial hypertension and dyslipidemia compared to those with no CAC (Table 1).

Multislice computed tomography coronary angiography findings. Based on MSCT coronary angiography, 54.1% (n=100) of the women had coronary atherosclerosis. Of these, 38.4% (n=71) had nonobstructive, and 15.7% (n=29) had obstructive CAD. The women with CAD were significantly older and had higher BMI compared to those with normal coronary angiography. The mean ages of women with no CAD, with non-obstructive and obstructive CAD were 53±12, 61±12, and 64±11 years and the mean BMI values were 21±5, 25±5, and 28±6 kg/m^2, respectively. Consistent with the CAC scoring results, women with CAD had higher prevalences of arterial hypertension and dyslipidemia compared to the normals (Fig. 1a, b). Moreover, the prevalence of hypertension was also significantly different between non-obstructive and obstructive CAD groups (Fig. 1b). Age (p<0.02) and arterial hypertension (p<0.05) were found to be the independent predictors of CAD detected by coronary angiography.

Plaque characterization was made on a segmental level based on MSCT angiographic properties. From the 1,583 analyzable segments (98% of total), 446 plaques were identified. Of these, 244 (54.7%) plaques were classified as noncalcified and 76 (17%) plaques were classified as stenotic.

There was a group of women who had no detectable CAC despite a positive coronary angiography. This subgroup comprised 41% (n=41) of all women with CAD (n=100). Of these women, 14.6% (n=6) had obstructive CAD, 19.5% (n=8) had a significant LAD plaque, and 36.6% (n=15) had plaques in three of the coronary arteries. Interestingly, there was no difference with regard to the prevalence of traditional risk factors between this group and the women who had both tests positive. However, the women with 0 CAC score and a positive coronary angiography were significantly younger compared to those with a positive CAC score and positive coronary angiography (mean age 57±11 *vs* 66±11 years, respectively; p<0.01). A representative coronary angiography of a woman who had 0 calcium score despite CAD diagnosed by MSCT angiography is shown in Fig. 2.

DISCUSSION

In our study population, all women were in low or intermediate-risk group based on the risk factors derived from the Framingham risk equations. However, we found that over one-third of them had detectable CAC; moreover, half of them had atherosclerotic plaques detected by MSCT angiography. According to the AHA primary prevention guidelines (based on traditional risk factor stratification), these women would not have been eligible for aspirin and statin therapy.[10] The MSCT results revealed that 15%

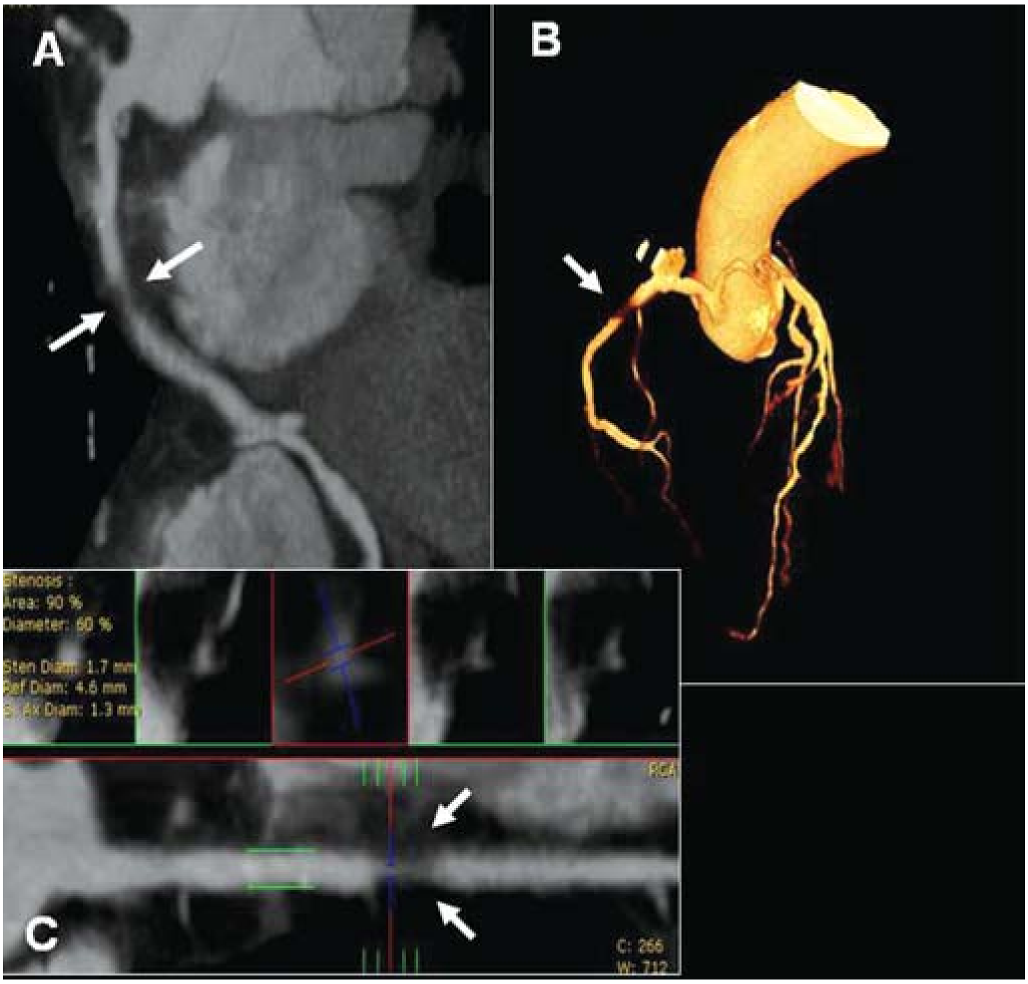

Figure 2. (A) Multislice computed tomography (MSCT) coronary angiographic image of a lesion in the right coronary artery in a study patient. Note the noncalcified plaque composition which was associated with a negative coronary artery calcium scoring. **(B)** The post-processed 3-dimensional view of the coronary arteries. **(C)** Automated quantification of the lesion stenosis yielded 60% luminal stenosis. Subsequent conventional coronary angiography confirmed the findings of MSCT angiography. Arrows indicate the stenotic segment in the right coronary artery.

of these women indeed required a more aggressive preventive strategy based on the estimated cardiovascular risk.[11-13]

There is considerable supportive evidence that CAC is an independent predictor of cardiac events and mortality, beyond traditional risk factor assessment.[11,12] Shaw et al.[13] reported in the largest cohort studied to date that the risk for cardiovascular death increased proportionally to the baseline CAC scores in both genders. When the same population was evaluated separately with regard to gender, a significantly higher mortality rate was observed for women at each level of CAC compared to men. Calcium scoring yielded a more accurate risk stratification for CAD compared to conventional risk stratification alone.[12,13] In line with these finding, we observed a significant number of women with detectable CAC, although they were classified as low or moderate risk based on traditional risk assessment.

Interestingly, in our study group, the prevalence of CAD detected with MSCT coronary angiography was higher than that found with CAC scoring. Moreover, 15% of these women had obstructive CAD. Our findings confirmed the rationale that plaques, which are not detected by CAC scoring, might even cause moderate to severe stenosis of the coronary arteries. It has been clearly demonstrated that CAC scoring is superior to the Framingham risk index in the prediction of CAD events.[14] However, CAC scoring may fail to detect soft plaques or mixed plaques. Lately, it has been confirmed that MSCT coronary angiography can detect CAD even at earlier stages with a higher accuracy than CAC scoring.[15,16] In line with these, we observed that the women having CAD without detectable CAC were significantly younger than those having higher CAC scores.

Very recently, Pundziute et al.[17] assessed the feasibility of MSCT coronary angiography with regard to gender. They reported that coronary angiography by MSCT in women was as accurate as in men. In our study, 98% of the segments were analyzable and the amount of our data yield was similar to theirs.

Women who had CAD diagnosed by either CAC score or MSCT coronary angiography showed significant differences with regard to traditional risk factors. Although there were no differences in the prevalences of family history of CAD and smoking between the women with and without CAD, age, BMI, and prevalences of hypertension and dyslipidemia were found to be higher in the former. Besides, age and hypertension were found as independent predictors of CAD. The close relationship between these atherosclerotic risk factors and CAD were clearly shown in several studies of CAC score and MSCT coronary angiography.[9,18]

Although our findings suggest that MSCT angiography is a more accurate way of risk stratification than by traditional risk assessment, screening every woman may not be feasible. Therefore, it is vital to identify a subset of women within the low or moderate risk group that presents an increased likelihood of having higher burden of coronary atherosclerosis. Based on our data, we believe that it may be reasonable to consider noninvasive detection of subclinical CAD with MSCT coronary angiography in asymptomatic women particularly with multiple risk factors even in the absence of coronary calcium.

Limitations. The study has some limitations that need to be addressed. Risk factors for CAD were self-reported and data on risk factors were collected as categories. Our use of risk factor categories instead of continuous variables may seem to be inadequate. However, in a recent re-analysis of the Framingham data, Wilson et al.[19] showed that the use of categories might be acceptable in assessing an individual's risk for cardiovascular events. Furthermore, self-reporting of risk factors has been shown to be reliable and accurate.[20] Therefore, we believe that the use of risk categories in our study is appropriate.

The size of the study population is relatively small compared to previous CAC scoring studies. However, different from those studies, we performed MSCT coronary angiography, which has been shown to be a more sensitive tool for CAD detection. Besides, it is important to keep in mind that this is not a general population-based screening study, and all the patients were self- or cardiologist-referred for cardiovascular risk assessment. Thus, a higher than expected prevalence is not surprising in the study group. However, as addressed in the discussion section and confirmed by our findings, a remarkable number of asymptomatic women with subclinical atherosclerosis are missed by 'traditional' risk factor assessment.

Finally, an important drawback of MSCT is the radiation dose that is still considerably high particularly when asymptomatic individuals are considered to be potential candidates. However, substantial decreases in the radiation dose can be achieved with the use of new filters.

In conclusion, assessment of atherosclerosis by MSCT coronary angiography may provide an incremental contribution to global risk assessment in identifying asymptomatic women who may benefit from more aggressive primary preventive therapy. Women with multiple risk factors, especially in the presence of older age and arterial hypertension, may be potential candidates for further risk stratification by MSCT angiography. Further prospective studies are needed in this group of individuals to determine the utility of MSCT findings in assessing CAD-related events over time.

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