



# Coronary Computed Tomography Angiography: Enhancing Risk Stratification and Diagnosis of Cardiovascular Disease in Women

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## Abstract

*Purpose of review* There are numerous gender- and sex-based differences that contribute to the increased morbidity and mortality related to atherosclerotic cardiovascular disease (ASCVD) in women. Early detection of risk and targeted management of atherosclerotic disease is fundamental to reduce ASCVD risk and improve outcomes in women. In this review, we examine the utility of cardiac computed tomography (CT) and coronary CT angiography (CTA) in three ASCVD scenarios including coronary artery calcium scoring for risk stratification in asymptomatic women, and coronary CTA for diagnosis and prognosis of stable ischemic heart disease and acute chest pain. The risks of radiation exposure and the potential applications of novel technologies in women are explored.

*Recent findings* CTA provides the capabilities of early recognition and management of nonobstructive coronary artery disease (CAD). Recent advancements in plaque composition and morphology further enhance the prognostic yield from coronary CTA. Innovations in stress perfusion and computational fluid dynamics allow for evaluation of physiological measures of ischemia. In addition, developments in artificial intelligence (AI) may also help unlock a deeper understanding of atherosclerosis and risk in women.

*Summary* Coronary CTA is an accurate and useful modality for early detection and management of ASCVD in women. Novel technologies hold great promise for furthering our understanding of sex-specific pathophysiology and potential improvement in clinical management and outcomes.

## Introduction

Cardiovascular disease is the leading cause of death in women in the USA, killing one in three women in 2018 [1]. Although mortality in women has declined over three decades by approximately 30%, the decline is far less compared with men, especially among women less than 55 years of age [1]. There are numerous gender- and sex-based differences that contribute to the increased morbidity and mortality related to atherosclerotic cardiovascular disease (ASCVD) in women. Sex-specific nontraditional ASCVD risk factors, such as the

post-menopausal state, gestational hypertension, and preterm labor go unaccounted for in risk stratification algorithms, resulting in diagnosis delays [2]. An increased interest in sex-specific nontraditional risk factors and the unique impact of traditional ASCVD in women has resulted in a growing understanding of mechanisms leading to poorer outcomes. Early detection of risk and targeted management of atherosclerotic disease is fundamental to reduce ASCVD risk and improve outcomes in women.

## Risk stratification and diagnostic evaluation in women

Diagnostic evaluation of ASCVD in women is challenging. Women often present with less exertional symptoms when compared with similarly aged men. These symptoms are often labeled as “atypical,” leading to misdiagnosis and delays in care. Women also present with cardiovascular disease (CVD) at an older age than men, with greater burden of ASCVD risk factors [3••]. In a large cohort of 2,363 asymptomatic women and men classified as low-intermediate Framingham risk score (10-year predicted risk of 6–9.9%), women were nearly 10 years older than their male counterparts [4]. There is now new understanding of the pathophysiology of CAD in women going beyond our established understanding of atherosclerosis, with more focus on sex- and gender-specific CVD research. CVD in women includes not only atherosclerotic obstructive CAD, but also an expanded spectrum of coronary disease, including coronary microvascular dysfunction (CMD), endothelial dysfunction, vasomotor abnormalities, spontaneous coronary artery dissection (SCAD), and stress-induced cardiomyopathy [3••].

Important pathophysiological differences of CVD in women is that they have (i) higher prevalence of angina, (ii) a lower burden of obstructive CAD on angiography, (iii) and a poorer prognosis when compared with men [5]. Additionally, current risk scores based on ACS thresholds and determined in predominantly male-based populations do not accurately predict risk in women. Subsequently, risk scores classify women as being at lower risk, further limiting accurate selection of at-risk women for aggressive preventive and therapeutic measures [6, 7]. There is thus the need for other forms of noninvasive risk stratification tools to improve prompt diagnosis, management, and follow-up in female populations [6].

Women have smaller epicardial coronary arteries and may develop hemodynamically significant and symptomatic stenoses, despite smaller absolute plaque burden. Evidence consistently reports that women referred for elective invasive coronary angiography are less likely to have obstructive CAD when compared to men [8–10]. Women's Ischemia Syndrome Evaluation (WISE) and other related studies have implicated abnormal coronary reactivity [11], microvascular dysfunction [12], and plaque erosion/distal microembolization [13, 14] as causative to female-specific IHD pathophysiology.

## Calcium scoring for risk stratification

The Coronary Artery Calcium Score (CACs) scan is a rapid, non-contrast CT scan of the heart performed with ECG-triggered acquisition. CAC scans performed according to SCCT acquisition guidelines achieve an effective radiation dose of < 1.0 millisievert (mSv). Coronary Artery Calcium Score is currently considered a valuable supplement to the Framingham Risk Score for the assessment of CVD risk in asymptomatic individuals [15]. It is a highly specific feature of coronary atherosclerosis and has emerged as a widely available, consistent, and reproducible means of assessing risk for major CVD outcomes in asymptomatic patients [15]. CACS refines assessments of a person's risk for CVD and identifies those who are most likely to benefit from preventative treatment [15]. In 2010, Polonsky et al. showed that the addition of CACS to a prediction model based on traditional risk factors significantly enhanced the classification of risk and placed more individuals in the most extreme risk categories [16]. Hence, demonstrating that CAC scores are incremental to traditional risk factors and integration of both sets of information can enhance risk assessment [15]. This added value of CAC over and above traditional risk factors for prediction of cardiovascular events has been demonstrated in several studies [17].

Several population-based cohort studies have also consistently demonstrated that elevated CAC scores are associated with increased risk of new-onset CVD, independent of standard risk factors and the Framingham Risk Score [18]. Increasingly, the location, number or extent, site (proximal, mid-, or distal segments), number of vessels, plaque density (in Hounsfield units), and the size and volume of CAC are important considerations for risk assessment [19, 20]. This is particularly important in women as nearly 60% of women with sudden cardiac death have no preceding symptoms, and post-infarction survival is lower for women than men [21]. This emphasizes the importance of early detection [22]. In a large cohort of 2,363 asymptomatic women and men classified as low-intermediate Framingham risk score (10-year predicted risk of 6–9.9%), women were nearly 10 years older than their male counterparts [23]. Women with CAC score of 0 had a low 15-year mortality of 5% compared with 23.5% for women with CAC score  $\geq$  400. Thus, providing long-term evidence that CAC is effective in identifying high-risk women who were otherwise deemed as low-intermediate risk by Framingham risk score [23]. Most recently, from the CAC consortium of 63,215 asymptomatic men and women, long-term cardiovascular mortality was similar between women and men without CAC, while detectable CAC was associated with 1.3

higher hazard for cardiovascular death among women when compared with men [24•]. Long-term prognosis across racial and ethnic subgroups of women and men varied based on CAC findings in the NIH-NHLBI-sponsored MESA cohort [23].

## Diagnostic accuracy of CTA in women

Diagnostic accuracy studies on CTA have consistently reported high sensitivity and negative predictive values, approaching 100%, for both women and men allowing for accurate exclusion of CAD [25, 26]. Although it is likely that arterial size impacts diagnostic specificity, evidenced by the lower values in women as compared with men (75% vs. 90%,  $p < 0.05$ ) [27], high diagnostic accuracy is preserved in women as demonstrated in sex-specific analyses from the Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY) and Combined Non-invasive Coronary Angiography and Myocardial Perfusion Imaging Using 320 Detector Computed Tomography (CORE320) trials [28, 29].

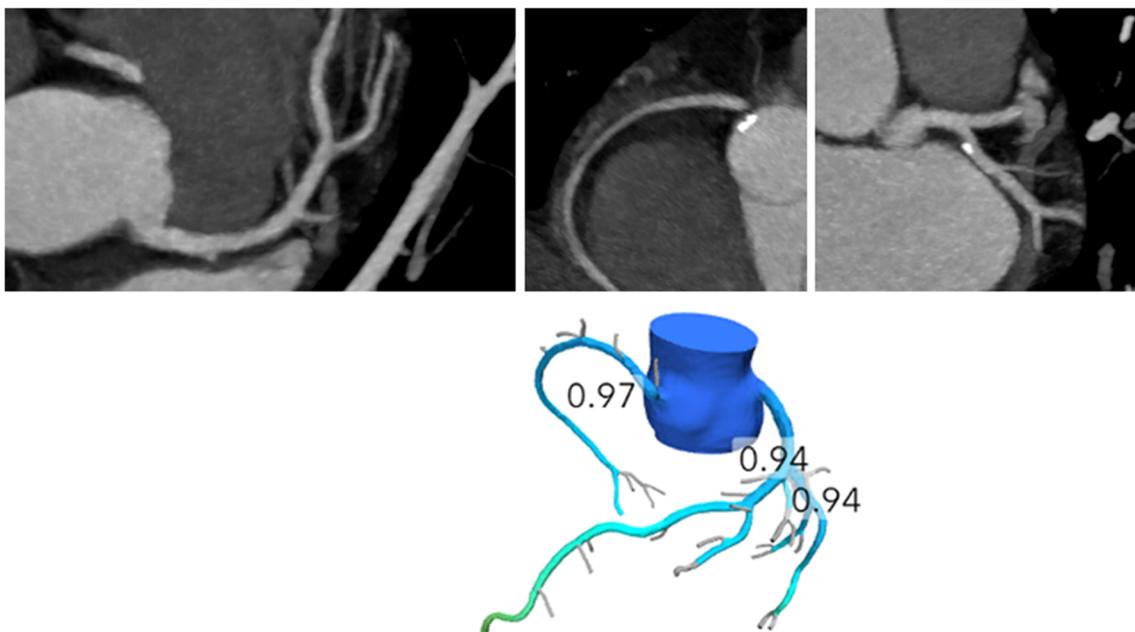
## Coronary CTA in women with chronic stable angina

When it comes to noninvasive testing for CVD, interpretation algorithms are often based on increasing age and typical angina symptoms. Since atypical symptoms are common in women, the lack of typical symptoms may contribute to delays in diagnosis. Additionally, tests designed to detect obstructive disease (> 70%) stenosis may be deceiving if negative, particularly because the mechanism of ongoing symptoms and death in the presence of non-obstructive disease is unclear. Coronary computed tomography angiography (CTA) provides the capabilities of early recognition and management of nonobstructive CAD, which is particularly important among women.

Coronary CTA improves patient outcomes compared with functional testing. Numerous large-scale randomized, controlled comparative effectiveness trials, such as PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain;  $n = 10,003$ ) and SCOT-HEART (Scottish Computed Tomography of the Heart;  $n = 4146$ ), have established that anatomic assessment with coronary CTA is at least as effective as other non-anatomic strategies for all studied cardiovascular outcomes [30, 31].

Among randomized controlled imaging-guided trials, coronary CTA has been consistently associated with reduced myocardial infarction (MI) in both acute and stable chest pain populations [27]. This is due to the impact that visualized coronary atherosclerosis on coronary CTA has on subsequent utilization of preventive therapies, such as aspirin and statins [27]. In SCOT-HEART, patients who underwent coronary CTA had a fourfold increase in the use of aspirin or statin therapy [31].

The advantage with coronary CTA over functional tests that detect only flow-limiting CAD is the accurate quantification of even non-critical disease, with opportunities for aggressive preventive measures. Generally, coronary CTA has a much higher diagnostic accuracy when compared with functional stress testing (Figures 1) [32].



**Fig. 1.** A 70-year-old woman presented to the office with left-sided chest pain lasting 10 min, relieved with rest and no associated symptoms. She is usually active with no exacerbating symptoms. Exercise stress echocardiogram results were equivocal with normal stress ECG findings, but a questionable hypokinesis in the distal anterior wall and apex on stress echocardiogram. Subsequent coronary CTA revealed a nonobstructive calcified plaque with 25–50% stenosis in the left circumflex artery. There was a focal calcification in the right sinus of Valsalva just anterior to the origin of the RCA and mild ostial narrowing. Otherwise, she had normal coronary arteries. Fractional flow reserve (FFR) values revealed low likelihood of functionally significant stenosis.

## Coronary CTA in women with acute chest pain

Approximately 55–85% of emergency department (ED) patients with chest pain do not have acute coronary syndrome (ACS) [33, 34] and typically will be classified as having intermediate or low risk of ACS. Available risk-stratification algorithms, which combine clinical and ECG findings, typically have not been considered accurate in identifying the low-risk group of patients who have a 30-day risk for major adverse cardiac events (MACE) of less than 1% and who thus can be discharged safely [34]. Early utilization of cardiac CTA in ED patients presenting with chest pain and low-to-intermediate risk of ACS quickly identifies a group of particularly low-risk patients (less than 1% risk of adverse events at 30 days), which allows safe and expedited discharge [35].

A number of randomized trials have shown that an early CTA strategy is safe and associated with reduced length of stay (LOS) as compared with the standard evaluation in the acute evaluation of chest pain in the ED. [36] In that regard, CTA is valuable in the acute setting for low-intermediate risk women in the ED. ROMICAT II trial found that women who undergo coronary CTA compared with standard cardiac evaluation had less hospital admissions, shorter LOS (13.6 h shorter in women versus vs. 2.2 h in men,  $p = 0.006$ ), and lower total radiation

dose compared with men [37]. The finding of women benefiting more from a strategy of early CTA is likely due to their lower CAD prevalence and severity. More than half (58%) of women had a normal CTA (vs. 37% for men,  $p < 0.0001$ ) and with less obstructive CAD (5% vs. 17%,  $p = 0.0001$ ) [37].

CTA also offers the additional advantage in the ED for women of detecting and treating nonobstructive CAD, which would have not otherwise been diagnosed.

## Plaque assessment by CTA

Pathophysiologic and invasive studies of patients following an acute coronary event demonstrate that plaque erosion is more common among women as compared with men, especially in younger women [38]. Plaque composition and morphology further enhances the prognostic yield from coronary CTA by detailing not only the extent of plaque burden, but also plaque characteristics associated with a higher risk of major coronary events. In the PROMISE trial, the presence of high-risk plaque (positive remodeling, low computed tomography (CT) attenuation, or napkin ring sign) was associated with significantly increased risk of major adverse cardiac events (adjusted hazard ratio 1.73; 95% confidence interval, 1.13–2.62), even after adjustment for risk factors and stenosis severity [6]. The prognostic importance of high-risk plaque was especially evident among subjects with nonobstructive CAD on CTA (adjusted hazard ratio 4.31 vs. 2.64) among this low-intermediate risk cohort (33% with 10-year ASCVD  $< 7.5\%$ ), which is more common in women [2, 6].

Recent evidence supports a female-specific profile of a smaller plaque burden and less obstructive CAD and often with worse clinical outcomes for women [39, 40]. These pathophysiologic profile differences among women and men support the importance of detecting both the presence of CAD and atherosclerotic plaque characteristics. CTA is a well-established diagnostic imaging modality and noninvasive procedure capable of identifying the burden of obstructive CAD and nonobstructive atherosclerosis. Given the greater burden of nonobstructive CAD in women, CTA is of unprecedented diagnostic value to guide prompt and effective treatment strategies that improve clinical outcomes.

For women, the detection of atherosclerotic plaque, even nonobstructive CAD, is critical for risk stratification purposes [41, 42]. From the COroNary CT Angiography Evaluation For Clinical Outcomes: An InteRnational Multicenter Registry (CONFIRM) registry, there was an association between increase MACE risk and nonobstructive CAD among 2,056 women ( $p < 0.001$ ), but no disparity between the sexes [41]. We know from the PROMISE trial that, at 2 years follow-up, high-risk atherosclerotic plaque was a stronger predictor of major adverse cardiovascular events (MACE) among women, more so than for men [42], with the adjusted hazard ratio being four-fold higher for women with versus without high-risk atherosclerotic plaque.

## Radiation exposure related to CTA

One concern with coronary CTA and women is radiation safety and as such, care should be taken to aggressively implement radiation dose reduction techniques.

With the new technological advances, there has been a significant decrease in radiation dose associated with coronary CTA [43]. Exposure to ionizing radiation is a concern for other imaging modalities such as myocardial perfusion imaging with SPECT, PET, and invasive coronary angiography (ICA). Based on clinical trial and registry observations, radiation exposure to SPECT imaging is substantially higher compared with CTA [44, 45]. The median effective dose for SPECT is  $\sim 10$  mSv [45]. PET imaging has a lower effective dose, in the 2–3-mSv range [46]. A diagnostic ICA has an average effective dose of  $\sim 7$  mSv [47]. From the CRESCENT trial, the median effective doses for CTA were 1.7 mSv in women and 2.6 mSv in men [48].

With regard to pregnancy, according to an American College of Obstetrics and Gynecology (ACOG), the use of coronary CTA should not be withheld in pregnancy if it is clinically indicated; however, the risks and benefits should be weighed and discussed prior to imaging [49]. The risk from radiation to the fetus is very low for CTA, which is mainly indirect scatter from within the imaged portion of the patient. There is currently no known evidence linking teratogenic, mutagenic, or other harm to the fetus [49, 50]. The use of iodinated contrast is not contraindicated in pregnant women, but should be limited to cases in which it is absolutely required to acquire the needed information. The ACOG also recommends that breastfeeding may be continued after iodinated contrast injections as  $< 1\%$  of iodinated contrast is excreted into the breast milk [49].

## Novel technologies

CTA has evolved greatly over the last decade with expanded applications and proven in the diagnosis and management of CAD, in guiding structural heart disease intervention and in the diagnosis and treatment of congenital heart disease. CTA has evolved from attempting to identify potential native coronary artery stenosis and bypass graft occlusion enabling imaging technology to play a crucial role in clinical decision-making across all aspects of cardiovascular medicine [51••].

Randomized trials have shown that a fractional flow reserve (FFR) threshold of 0.80 distinguishes patients and lesions that will and will not benefit from coronary revascularization [52]. FFR has therefore emerged as the reference standard for guiding coronary revascularization in intermediate-range lesions. Noninvasive anatomic assessment using CTA reveals high diagnostic performance for detection or exclusion of CAD. However, coronary CTA tends to overestimate obstructive CAD, and the correlation of stenoses to downstream myocardial ischemia is poor.

Advances in computational fluid dynamics and individual image-based modeling permit calculation of coronary blood flow and pressure from standard acquired coronary CTA datasets [53–55]. This technique allows for non-invasive calculation of FFR. Prospective multicenter trials that included patients with known or suspected CAD and blinded comparison with FFR and FFR<sub>CT</sub> exhibited a high and superior diagnostic performance compared with stenosis assessment on coronary CTA alone [53]. The short-term 90-day outcomes data from the ADVANCE (Assessing Diagnostic Value of Non-invasive FFR<sub>CT</sub> in Coronary Care) Registry showed that FFR<sub>CT</sub> modified treatment recommendations in a large majority of patients as compared with coronary CTA alone [56].

One-year data from the international ADVANCE (Assessing Diagnostic Value of Non-invasive FFR<sub>CT</sub> in Coronary Care) Registry of patients undergoing CTA and FFR<sub>CT</sub> revealed that downstream clinical management is significantly different among groups depending on stenosis severity and FFR<sub>CT</sub> value [57••]. There was a trend toward lower MACE and significantly lower cardiovascular death or MI in patients with a negative FFR<sub>CT</sub> compared with patients with abnormal FFR<sub>CT</sub> values [57••].

Currently, a single vendor of FFR<sub>CT</sub> dominates the field of computational flow dynamics (CFD) in cardiovascular imaging because of its established evidence base and Food and Drug Administration (FDA) and NICE approval, in the USA and UK, respectively. However, other CFD protocols are also emerging, with validation of several alternatives recently published [51••].

FFR<sub>CT</sub> may also contribute to our understanding of the incompletely understood entity, microvascular angina (MVA). Coronary microvascular disease (CMVD) is characterized by an impaired microvascular and suboptimal coronary vasodilator response to exercise or pharmacological stress [58]. Microvascular dysfunction and diffuse coronary atherosclerosis without obstructive lesions are more prevalent in women than in men [29]. Patients with MVA demonstrate a significantly lower coronary CTA-derived coronary V/M ratio than asymptomatic controls [59].

Given the important gender differences in gender-related risk factors, diagnosis, and management of CVD, there is an increasing need for gender-specific data to help guide diagnosis and management. Further advancements in CTA in regard to coronary perfusion have improved the diagnostic accuracy of obstructive CAD in women [29]. The CORE320 trial (Coronary Artery Evaluation Using 320-Row Multidetector Computed Tomography Angiography and Myocardial Perfusion) revealed that the combination of CTA and coronary CT perfusion (CTP) accurately identifies patients with flow-limiting coronary lesions [60]. Follow-up studies have shown CTP has incremental value over CTA alone in women, which was not the case in men, which may be related to the underlying sex differences in CVD [29].

Artificial intelligence (AI) is also an exciting advancement in imaging that may help unlock a deeper understanding of atherosclerosis and risk in women. Specific subsets of AI, machine learning (ML) and radiomics, are able to integrate an extremely large number of input variables to explore all available data for nonlinear relationships associated with outcomes. They can also extract various quantitative features from a region of interest to create large datasets in which each abnormality is described by parameters that extend far beyond the ability of the human eye or mind [61].

## Conclusion

CVD in women is challenging due to gaps in understanding of sex- and gender-specific factors that contribute to delays in diagnosis as well as timely and effective prevention and therapy. Coronary CTA is an accurate and useful modality for early detection and management of CVD in women. Novel technologies hold great promise for furthering our understanding of sex-specific pathophysiology, which in turn could result in improved CVD outcomes in women.

## Compliance with Ethical Standards

### Conflict of Interest

Sara Karnib reports institutional grant support from Heartflow, Inc.

Kavitha M. Chinnaiyan reports institutional grant support from Heartflow, Inc. and is on the medical advisory board of Heartflow, Inc.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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