Guidelines

Coronary computed tomographic imaging in women: An expert consensus statement from the Society of Cardiovascular Computed Tomography

ARTICLE INFO

ABSTRACT

This expert consensus statement from the Society of Cardiovascular Computed Tomography (SCCT) provides an evidence synthesis on the use of computed tomography (CT) imaging for diagnosis and risk stratification of coronary artery disease in women. From large patient and population cohorts of asymptomatic women, detection of any coronary artery calcium that identifies females with a 10-year atherosclerotic cardiovascular disease risk of > 7.5% may more effectively triage women who may benefit from pharmacologic therapy. In addition to accurate detection of obstructive coronary artery disease (CAD), CT angiography (CTA) identifies nonobstructive atherosclerotic plaque extent and composition which is otherwise not detected by alternative stress testing modalities. Moreover, CTA has superior risk stratification when compared to stress testing in symptomatic women with stable chest pain (or equivalent) symptoms. For the evaluation of symptomatic women both in the emergency department and the outpatient setting, there is abundant evidence from large observational registries and multi-center randomized trials, that CT imaging is an effective procedure. Although radiation doses are far less for CT when compared to nuclear imaging, radiation dose reduction strategies should be applied in all women undergoing CT imaging. Effective and appropriate use of CT imaging can provide the means for improved detection of at-risk women and thereby focus preventive management resulting in long-term risk reduction and improved clinical outcomes.

Among women of diverse ages, atherosclerotic cardiovascular disease (ASCVD) has been a leading cause of morbidity and fatal outcomes for many decades.[1,2] Overall ASCVD mortality has declined by approximately 30% but is far less for women as compared to men.[3] Although marked declines in mortality have been reported, sizeable detection gaps remain and more recent trends document a concerning increasing prevalence of ASCVD among middle-aged women.[1,2] Thus, for women of all ages, early detection of risk and targeted treatment is foundational to reduce ASCVD risk and improve outcomes.

Overall, women have a higher prevalence of chest pain and diminished quality of life when compared to men.[4] The diagnostic evaluation of women is challenging as women often present with less exertional and more stress related symptoms when compared with similarly-aged men. They also are on average older with a greater burden of ASCVD risk factors.[5,6] All risk scores classify women as being at lower risk and this further hampers optimal selection of at-risk women.[6–9]

There is some evidence of a sex-specific profile unique to women with regards to atherosclerosis variants.[10–12] Pathophysiologic and invasive studies of patients following an acute coronary event demonstrate that plaque erosion is more common among women as compared to men, especially in younger women.[13] Conversely, a ruptured atherosclerotic plaque, associated with thin cap fibroatheroma, is more frequent in men than women, which suggests a protective mechanism related to women's premenopausal status.[13] To date, the evidence supports a female-specific profile of a smaller plaque burden and less

obstructive coronary artery disease (CAD) and often with worse clinical outcomes for women.[14–18] These varied profiles among women and men support the importance of detecting both the presence of obstructive CAD as well as potential precursor atherosclerotic markers unique to women.

CTA is now a well-established diagnostic imaging modality and the lone noninvasive procedure capable of identifying the burden of obstructive CAD and nonobstructive atherosclerosis. Given the greater burden of nonobstructive CAD in women, CTA has the potential to improve diagnostic certainty and guide prompt and effective treatment strategies that improve clinical outcomes. In this expert consensus statement from the SCCT, we provide a synthesis of evidence and clinical recommendations for the appropriate use of CT imaging in women. Moreover, we will cover the evaluation of asymptomatic and (stable and acute low-intermediate risk) symptomatic women and highlight the unique evidence as to the role of CT imaging. We conclude with a section on radiation dose reduction techniques and imaging of the pregnant woman.

1. Risk stratification of asymptomatic women using coronary artery calcium (CAC) scanning

The CAC scan is a rapid, non-contrast CT scan of the heart performed using prospective ECG-triggered acquisition. CAC scans performed according to SCCT acquisition guidelines achieve an effective radiation dose of < 1.0 millisievert (mSv), a dose comparable to
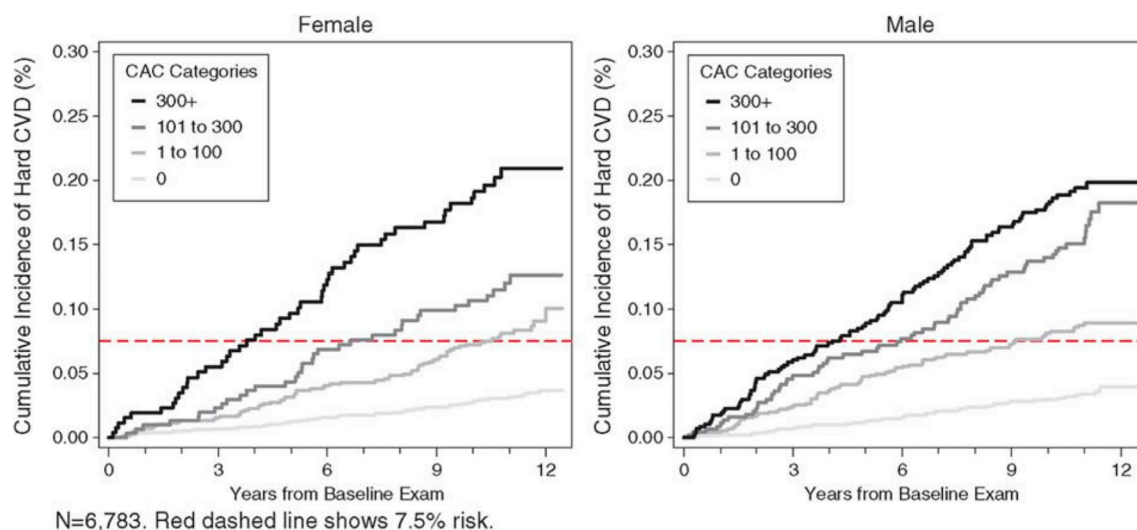
Fig. 1. 10-Year Cumulative Incidence for Major CVD Events by CAC Score Categories in Women and Men from the NIH-NHLBI-Sponsored Multi-Ethnic Study of Atherosclerosis (MESA). Reprint from Budoff et al.[47]

screening mammography.[19] CAC scanning can be accurately performed with newer CT scanners using single-beat acquisition methods yielding even lower radiation doses (< 0.4 mSv), with further dose reductions achievable using contemporary iterative reconstruction techniques.[20–22]

Calculation of the Agatston score has been shown to be an accurate measure of the overall coronary atherosclerotic burden.[23,24] Increasingly, the location, number or extent, site (proximal, mid-, or distal segments), number of vessels, plaque density (in Hounsfield Units), as well as the size and volume of CAC are important considerations for risk assessment.[25,26] The Agatston score may be reported as a percentile of severity as compared to age, gender, and ethnicity-matched individuals, as determined from the Multi-Ethnic Study of Atherosclerosis (MESA).[27] Additional methods of quantifying CAC that do not account for lesion density (mass or volume scores) may have higher reproducibility and may better assess cardiovascular risk, but are not commonly utilized clinically, as the majority of studies evaluating the prognostic accuracy of CAC were performed using Agatston scoring.[28,29]

Importantly, nearly 60% of women with sudden cardiac death have no preceding symptoms and post-infarction survival is lower for women than men.[30] This emphasizes the importance of early detection. ACC/AHA's current standardized approach to guide primary prevention is based on a global risk score, the pooled cohort equation (PCE) for risk stratification and identification of patients eligible for preventive therapies.[31,32] The PCE and other risk scores are imprecise in women until significantly later in life as compared to men[33,34]; highlighting the potential for CAC scanning to provide a more precise risk assessment and guide earlier use of preventive care in women. In a large cohort of 2363 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.[35] Women with CAC score of 0 had a low 15-year mortality of 5% compared to 23.5% for women with CAC score ≥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.[35] 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 to men.[36] Additionally, women with larger sized and more numerous CAC lesions had 2.2-fold higher cardiovascular death as compared to men.[36]

Numerous large-scale studies have repeatedly shown that CAC scanning improves risk detection over and above standard risk factor scores, such as the PCE, for women and men.[37–42] The value of more accurate ASCVD risk assessment allows women and their providers to make more informed choices as to appropriateness of lifelong preventive therapies, such as aspirin, statins, and hypertensive treatment as well as to improve compliance with therapeutic lifestyle changes. While women have less CAC than men, with calcification appearing nearly a decade later, CAC scanning identifies those at highest risk, regardless of a low 10-year or lifetime risk score.[35,43,44] A recent meta-analysis of 5 large population-based cohorts of women (n = 6739) with an ASCVD risk < 7.5% (group in whom statin therapy would not be typically recommended) demonstrated that CAC was present in 36% of women and any CAC conveyed a 2-fold increased risk of incident ASCVD, even among this lower-risk cohort.[45] Importantly, subjects with a CAC score of 0 have been consistently shown to be at very low risk, with a ~0.11% annual or 1.1–1.5% 10-year risk of incident CAD events, independent of risk factors. The absence of CAC reclassifies up to half of patients who were recommended to start statin therapy based on their PCE risk score; with the potential to avert the use of statins due to their observed low risk status.[46]

Long-term prognosis across racial and ethnic subgroups of women and men varied based on CAC findings in the NIH-NHLBI-sponsored MESA cohort.[47] For women, the 10-year CVD event rates were 2.8%, 7.3%, 10.6%, and 19.0%, respectively, for CAC scores of 0, 1–100, 101–300, and > 300 (Fig. 1). Similar findings were reported in men. Of importance, women and men with a CAC score > 100 had an ASCVD event rate > 7.5%, the threshold for statin treatment. While the AHA/ACC 2013 guideline recommends initiating statin therapy for absolute calcium score of ≥300 or ≥75th percentile for age, sex, and ethnicity,[48] perhaps an alternative strategy would be to initiate statin with a lower calcium score of burden if the ASCVD event rate is > 7.5%.

1.1. Summary

The evidence is robust that CAC scanning more accurately characterizes risk in women. It is common to employ CAC scanning in women at intermediate CVD risk (or slightly below this threshold, given the older age of onset of ASCVD in women relative to men). As well, CAC scanning should be considered in women whose risk score is inconsistent with perceived clinical risk and for women who request additional information regarding their CVD risk during shared decision making discussions with their physician.

2. Breast arterial calcification (BAC)

BAC, calcification of the arterial media (and occasionally intima) layer in breast arteries, is commonly visualized on screening mammography and has been associated with the presence of CVD risk factors and increased rates of major CVD events. A recent meta-analysis involving > 75,000 women demonstrated that ~13% have BAC on screening mammography and that any BAC was associated with increasing age, diabetes, and parity.[49] Interestingly, in healthy screening subjects, BAC was lower in smokers and not associated with hypertension, obesity, and dyslipidemia, suggesting that the mechanism of predominately medial calcification in BAC may be different than calcification seen in the epicardial coronary arteries. Nonetheless, the presence of BAC was associated with an increased risk of ASCVD events (adjusted hazard ratio: 1.32–1.44); although there are three longitudinal studies that largely used older, plain film mammography. Recently, investigators attempted to quantify severity of BAC (scale 0 to 12) using modern, digital mammography in 292 women who also underwent CAC scanning.[50] While any BAC (> 0) had only a modest sensitivity of 60% for its relationship to patients with detectable CAC (CAC > 0), higher degrees of BAC (> 4) increased the odds of detectable CAC by as much as 3-fold. Fig. 2 illustrates a woman with BAC and coronary artery calcifications.

2.1. Summary

Women with BAC may benefit from CAC scanning for further risk detection and to guide preventive care decision making.

3. Evaluation of women with stable chest pain (or equivalent) symptoms

In this section, we will discuss the accuracy of CTA for detection of obstructive CAD as well as highlight CTA's unique ability to identify prevalent, nonobstructive atherosclerosis in women. For this latter point, the detection of nonobstructive atherosclerosis is key given its importance in detailing not only the extent of plaque burden, but also plaque characteristics associated with an elevated risk of major coronary events.

3.1. Diagnostic accuracy of CTA for detection of obstructive CAD

The diagnostic evaluation of stable chest pain is largely undertaken for detection of obstructive CAD. Relevant to this discussion about invasive coronary angiography (ICA) and CTA, women have smaller epicardial coronary arteries and may develop hemodynamically significant and symptomatic stenoses, despite smaller absolute plaque burden. Decades of evidence consistently reports that women referred for elective ICA are less likely to have obstructive CAD when compared to men.[10–12,51,52] The frequent documentation of nonobstructive CAD and the non-trivial procedural complication risk (i.e., 3–4% among lower risk patients)[53] with ICA support noninvasive CTA as potentially safer for women. CTA with its spatial and temporal resolution has allowed for accurate assessment of the coronary arteries when compared to the gold standard, ICA.

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.[54–56] The 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.[57,58] Importantly, diagnostic accuracy is comparable in women and men, even when they were at low-intermediate pretest risk.[59]

While the strength of CTA is its high sensitivity and negative predictive value, specificity and positive predictive value remain variable.[54–56] However, the sensitivity for detecting stenosis in women was lower than men in smaller, distal segments (56% vs. 85%, p < 0.05) and side branches (54% vs. 89%, p < 0.001).[60] Arterial size likely also impacts diagnostic specificity which has been shown to be reduced among women as compared to men (75% vs. 90%, p < 0.05).[60] Importantly, CTA has a much higher diagnostic accuracy when compared to functional stress testing.[61]

3.2. CTA versus Functional Testing

In a large series of 375,886 patients (nearly half were women) from the American College of Cardiology's CathPCI™ Registry, women were more likely than men to have nonobstructive disease on ICA, even among those with prior abnormal stress test findings.[53,62] For ICA patients with prior diagnostic testing, patients undergoing CTA have a higher proportion of obstructive CAD on ICA as compared to stress testing; suggesting its utility in more appropriate selection for invasive testing.[62] These findings were replicated in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial where CTA was associated with lower rate of ICA with nonobstructive disease compared to stress testing (27% vs. 53%).[63] CTA also resulted in an increased certainty of diagnosing angina and prompt initiation of medical therapy (23% vs. 5%, p < 0.0001), as based on findings from the Scottish COmputed Tomography of the HEART (SCOT-HEART) trial.[64] The abundant findings that CTA leads to a greater initiation and intensification in preventive therapies is a strength of the modality as a guide to optimal medical management of patients; with rates of therapeutic intervention higher than that for stress testing.[65,66]

In a sex-specific analysis from the PROMISE trial, women more often had abnormal findings on stress testing as compared to CTA (12%
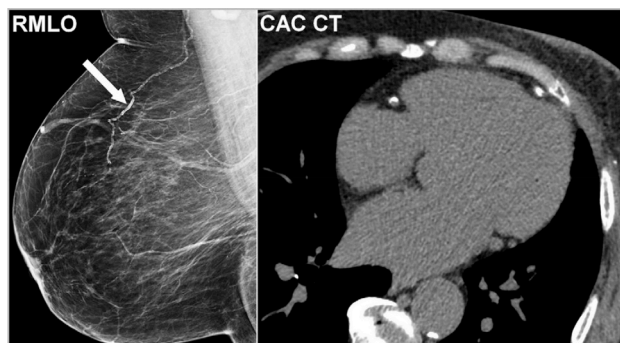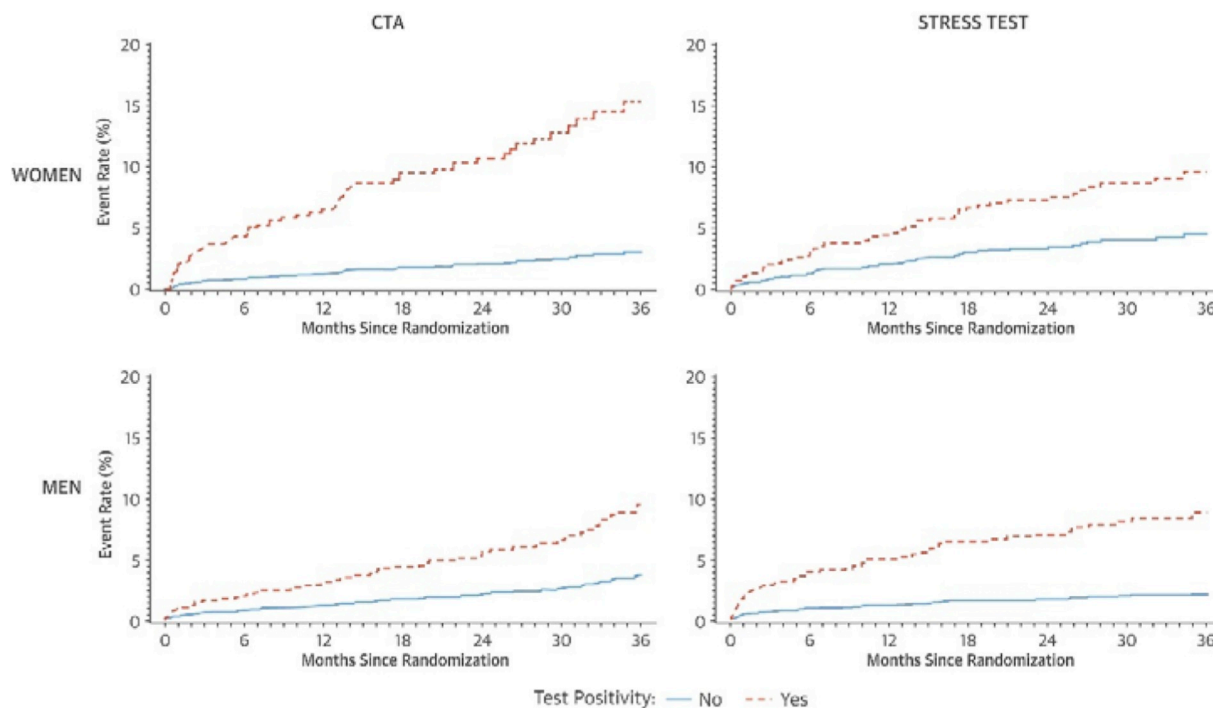

Fig. 2. Illustrative Case of a Woman with BAC and CAC. Right Mediolateral Oblique (RMLO) view of screening mammography shows vascular calcifications (arrow). In this patient, a non-contrast CT scan demonstrates CAC in the right coronary artery and left anterior descending coronary arteries. Courtesy of Suhny Abbara, MD. UTSouthwestern Medical Center.

Fig. 3. Cumulative Incidence of the Primary Outcomes in the PROMISE Trial Among Women and Men Based on Test Positivity. Among women, the adjusted hazard ratio for an abnormal CTA was 5.9 as compared to 2.3 for an abnormal stress test (p = 0.028). No differences were identified for men. Reprint from Pagidipati NJ et al.[68].

vs. 8%).[67,68] Additionally, CTA was more effective at risk stratification of women when compared to stress testing (Fig. 3).[68] In women, an abnormal CTA had a higher adjusted hazard ratio for major adverse cardiovascular events of 5.9 as compared to 2.3 for stress testing (p = 0.028); while no differences in risk stratification were noted for men.[68]

In the Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease (CRESCENT) trial, patients with stable angina were randomized to CAC scanning followed by selective CTA in those with detectable calcium on calcium score versus stress testing, which mostly exercise ECG testing.[69] Women showed greater benefit in reduction of time to final diagnosis and a reduced need for additional testing.[69] Women randomized to the CT arm required additional testing in 8% of cases as compared to 47% of women allocated to stress testing.[69]

3.2.1. Summary

CTA has a high predictive accuracy for identification of obstructive CAD and is demonstrated to be at least equally effective as stress testing. Thus, CTA can be used as a frontline procedure for evaluation of stable chest pain. For lower risk women, starting with CAC scanning may be helpful for risk stratification and as a gatekeeper to CTA.

3.3. Importance of detecting nonobstructive, atherosclerotic plaque in women

A large proportion of women with nonobstructive CAD (Fig. 4A) have a burden of significant atherosclerotic plaque which increases their ASCVD risk. From the NIH-NHLBI-sponsored Women's Ischemia Syndrome Evaluation, 80% of women with nonobstructive CAD had evidence of atherosclerosis by IVUS.[70] A challenge with the prior literature is that often patients classified as having nonobstructive CAD includes those with no plaque as well as those with atherosclerotic plaque resulting in mild luminal narrowing (1–49% stenosis). Careful subgrouping of those with normal coronaries as compared to those with nonobstructive atherosclerosis is foundational for targeted preventive care of women. Thus, in our discussion, the term nonobstructive CAD does not include those with normal coronaries.

CTA atherosclerotic plaque characterization offers unique insight into its extent and severity, composition, arterial remodeling, and the presence of high-risk features (Fig. 4B), such as, low attenuation plaque, positive remodeling, spotty calcium, and the napkin ring sign. In accordance with prior intravascular imaging studies, women had a smaller coronary luminal area, smaller plaque burden, and remodeling index, lower prevalence of thin cap fibroatheroma but with a similar prevalence of non-calcified plaque.[71] Similarly, by CTA, women generally have a smaller atherosclerotic plaque size and burden, as reported in multiple series.[5,71–75] In a study of asymptomatic patients, women had lower total plaque (by 23%) and non-calcified plaque (by 21%) volume as compared to men and this difference persisted after adjustment for traditional risk factors.[76] Similarly, lower calcified and non-calcified plaque volume in women was maintained across age subgroups from 40 to 74 years.[77]

For women, the detection of atherosclerotic plaque, even nonobstructive CAD is critical for risk stratification purposes.[78,79] Several series have focused on the longterm risk of nonobstructive atherosclerotic plaque in women and men. 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 2056 women (p < 0.001) but no disparity between the sexes.[78] From the PROMISE trial, 1 in 10 women had high risk plaque features of low attenuation plaque or positive remodeling.[79] At 2-years of follow-up, high risk atherosclerotic plaque was a stronger predictor of major adverse cardiovascular events among women, more so than for men. From PROMISE, the adjusted hazard ratio was 4-fold higher for women with versus without high risk atherosclerotic plaque (Fig. 5). Additionally, the extent and amount of nonobstructive plaque have been associated with increased cardiovascular death and myocardial infarction in both women and men.[80]
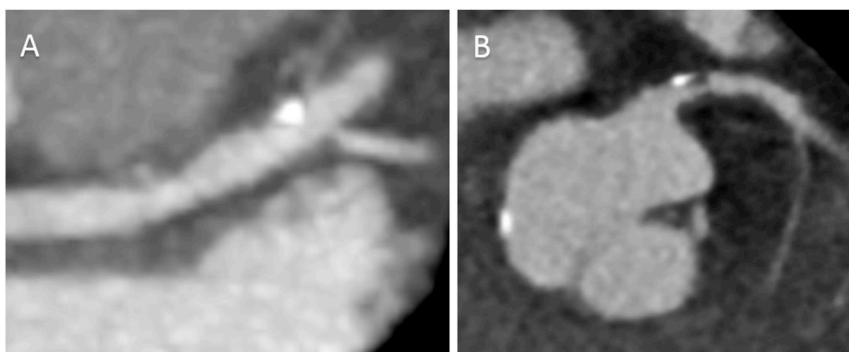
Fig. 4. Examples of Atherosclerotic Plaque Morphology. A. Nonobstructive coronary atherosclerosis with partially calcified plaque and mild (24–49%) luminal narrowing. B. Focal severe (> 70%) stenosis with features of high-risk plaques (low attenuation and spotty calcification). Courtesy of Sarah Rinehart, Piedmont Healthcare.

3.3.1. Summary

While women have less frequent obstructive CAD, CTA allows for the detection of nonobstructive plaque, its extent, and high-risk features. These components are important to identify in women and should prompt intensified preventive care and lifestyle modifications.

4. Evaluation of low-intermediate risk women in the emergency department (ED)

Candidates for imaging in the ED include those with suspected acute coronary syndrome (ACS) but with an initial non-ischemic ECG and negative troponin leading to categorization into low-intermediate risk based on one of several risk scores (e.g., History, Electrocardiogram, Age, Risk factors, and Troponin [HEART] score).[81–83] A number of randomized trials, such as Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment,[84] American College of Radiology Imaging Network-Pennsylvania,[85] and Rule Out Myocardial Infarction using Computer Assisted Tomography [ROMICAT] II,[86] have provided evidence that an early CTA strategy is safe and associated with reduced length of stay (LOS) as compared to the standard evaluation in the acute evaluation of chest pain in the ED.[87] In the observational ROMICAT I trial, CTA was highly sensitive and specific for detection of obstructive CAD among women < 65 years of age (sensitivity = 100% and specificity > 87%).[88] In the follow-up, multicenter ROMICAT II trial (Fig. 6), women had a greater reduction in LOS than men when CTA was used as compared to standard evaluation (13.6 hours shorter in women versus [vs.] 2.2 hours in men, interaction p = 0.006).[89] 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).[89] While there are no long-term sex-specific analyses for acute chest pain patients, absence of CAD by CTA provides a 2-year CAD event-free time period,[90] which can be very reassuring for women undergoing CTA and have normal studies.

Several studies have evaluated the role of CAC scanning in the acute evaluation of chest pain, largely focusing on lower risk patient subgroups.[91–93] Interestingly, in a pooled analysis of 2392 patients from the ACRIN PA and ROMICAT II trials, 4 patients (all women) with a CAC = 0 also had a diagnosis of ACS (0.5%, 95%CI: 0.1%–1.3%), while no men with CAC = 0 had ACS (0.0%, 95%CI: 0.0%–1.1%).[94] This may be due to the advanced age of women but may also suggest a burden of noncalcified plaque not detected by CAC imaging alone (Fig. 7).

4.1. Summary

CTA can be an important and safe diagnostic strategy in reducing length of stay in low to intermediate risk women presenting to the ED with symptoms concerning for ACS.

5. Special conditions that impact the evaluation of symptomatic women

5.1. Spontaneous coronary artery dissection (SCAD)

SCAD is an increasingly recognized cause of ACS that is typically observed in young to middle aged women without underlying atherosclerosis. Although its true prevalence remains uncertain, reviews
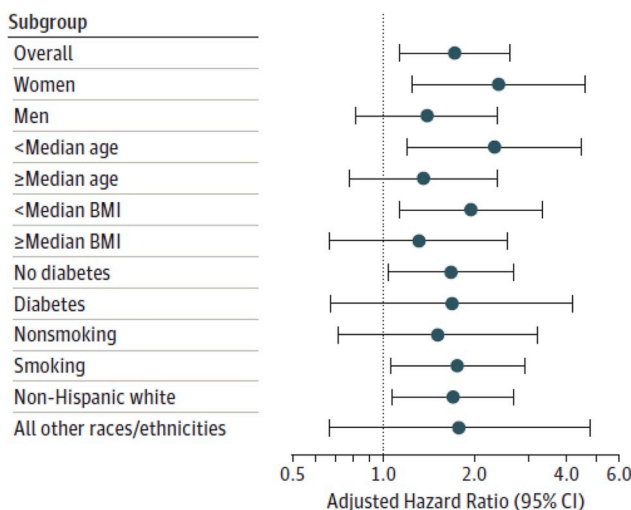
Fig. 5. Multivariable Analyses Estimating Major CAD Events in Women and Men with versus without High Risk Atherosclerotic Plaque: Results from the PROMISE Trial. Reprint from Ferencik et al.[79].
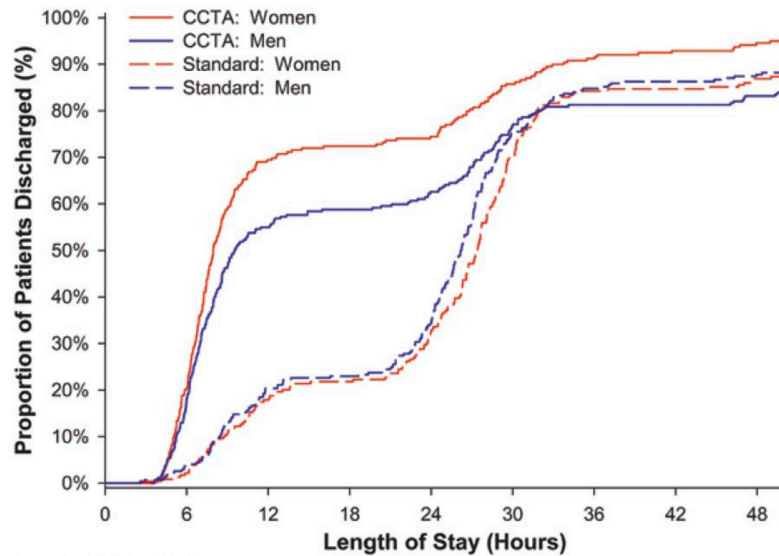
Fig. 6. Women had shorter length of stay (LOS) compared with men when an early cardiac computed tomographic angiography (CCTA) strategy was implemented randomized against standard emergency department (ED) evaluation: Results from ROMICATII-Trial. Reprint from Truong et al.[89]

suggest that the prevalence of SCAD is 1–4% among women with ACS.[95] Implicated etiologies include predisposing arteriopathy, peripartum states, connective tissue disorders, as well as physical or emotional stressors as precursors.[95,96] Studies have documented a high prevalence of fibromuscular dysplasia and coronary artery tortuosity in patients with SCAD.[95,97–99] The precipitating mechanisms include either dissection of or hemorrhage into the arterial wall which ultimately leads to true lumen compression and resultant myocardial ischemia, infarction, or sudden cardiac death. Imaging is useful to discriminate SCAD from ACS due to atherosclerotic disease.

While CTA has shown variable success at identifying SCAD, it has an advantage over invasive strategies since it does not cause or propagate a dissection if present.[96,100,101] Diagnosis is contingent upon identification of an intimal flap (Fig. 8) and/or the presence of intramural

hematoma; however these findings may be subtle and difficult to identify (especially when small distal arteries are affected) and may be misinterpreted as motion artifact, thrombus, or atherosclerosis.[96,100] Therefore, a negative CTA or ICA does not exclude the diagnosis of SCAD in patients with an appropriate clinical scenario. Further imaging evaluation with modalities possessing higher spatial resolution such as optical coherence tomography or intravascular ultrasound (IVUS) may prove superior for diagnosis.

5.2. Takotsubo cardiomyopathy (stress cardiomyopathy)

Takotsubo cardiomyopathy, also known as Takotsubo syndrome or stress cardiomyopathy, is characterized by a transient, reversible ventricular wall motion abnormality that extends beyond a single coronary

Fig. 7. A woman with ACS and calcium score of zero. (A) CTA showed severe (> 70%) stenosis with exclusively noncalcified plaque in the proximal LAD, and (B) corresponding invasive coronary angiography. Courtesy of Sarah Rinehart, Piedmont Healthcare.
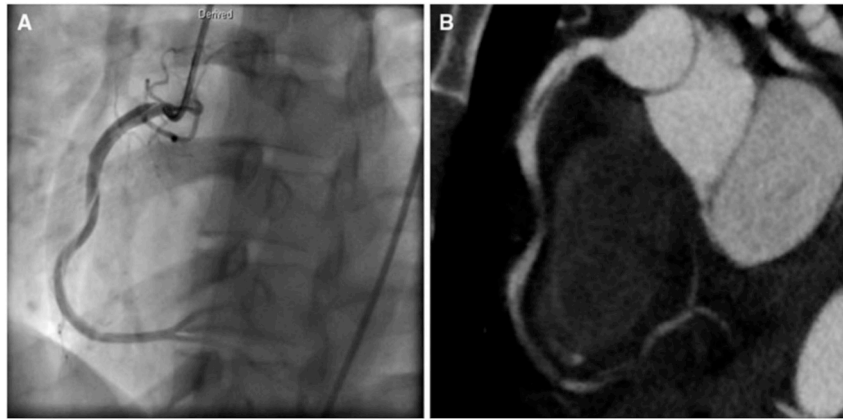
Fig. 8. Example of a right coronary artery (RCA) dissection in a woman with chest pain and non-ST elevation myocardial infarction. The intimal (or dissection) flap extends from the proximal to mid RCA in the invasive coronary angiography (A) and the corresponding coronary CT angiography (B). Reprint from Mousavi et al.[125].

artery territory and typically presents with end-systolic apical ballooning and mid-ventricular constriction that resembles its namesake, a Japanese octopus trap. Takotsubo cardiomyopathy is most commonly observed among post-menopausal women. A study of 6837 patients enrolled in the Nationwide Inpatient Sample Database revealed that women had an 8.8-fold higher odds of developing Takotsubo cardiomyopathy than men.[102] Moreover, that women > 55 years old were nearly 5-times more likely to develop Takotsubo cardiomyopathy than younger women. Our current knowledge remains incomplete and the pathophysiology remains uncertain, but systemic physiologic responses to endogenous or exogenous catecholamines and consecutive vasoconstriction with peripheral myocardial hypo-perfusion appear to have a crucial role as an emotional or stressful trigger is commonly present.[103]

The critical role of clinical assessment and diagnostic imaging is to differentiate Takotsubo cardiomyopathy from an ACS, as patients can present with similar clinical scenarios including with Troponin elevation. CTA acquired throughout the cardiac cycle enables assessment of both the coronary arteries and ventricular function. Classically, Takotsubo cardiomyopathy is manifested as hypokinesis or akinesis of the mid and apical left ventricular segments which extends beyond the left anterior descending artery. Although the apical left ventricular segment is most commonly affected (~82%), mid-ventricular (~15%), basal (~2%), and focal (~1%) patterns can also occur.[104] Right ventricular involvement may also be seen. Characteristically, patients with Takotsubo cardiomyopathy have minimal or no CAD on CTA; however, the presence of CAD does not preclude its diagnosis.[105]

6. Radiation safety

Exposure to ionizing radiation is a primary safety concern for CT in women; particularly concern with breast exposure.[106] For a 60 year old woman, the lifetime attributable risk (LAR) of cancer is 0.22% (1 in 466) after undergoing a CT of the heart; although these estimates are based on higher effective doses than commonly used today.[106] Contemporary, dose reduction techniques decrease these risk estimates substantially. Technological advances such as ECG based tube current modulation, prospectively ECG triggered scanning, iterative reconstruction, single-heartbeat and high-pitch helical scanning as well as body mass index- and heart rate-dependent protocols have resulted in significant decreases in radiation dose associated with cardiac CT (Supplemental Section 1).[107] In an anthropomorphic phantom study, the absorbed breast dose with retrospective ECG-gated helical, 64-slice CT performed without dose modulation was 82.9 mGy, decreasing by 79% to 17.5 mGy with 320-row scanning and dose modulation.[108] Exposure to ionizing radiation is a concern for other imaging modalities such as myocardial perfusion imaging with SPECT, PET, and

invasive coronary angiography. Radiation exposure to the commonly performed SPECT imaging is substantially higher than compared to CTA; based on clinical trial and registry observations.[109,110] The median effective dose for SPECT is ~10 mSv.[110] PET imaging has a lower effective dose, in the 2–3 mSv range.[111] A diagnostic, invasive coronary angiogram has an average effective dose of ~7 mSv.[112] From the CRESCENT trial, the median effective dose for CT was 1.7 mSv in women and 2.6 mSv in men.[113]

6.1. Breast shielding and displacement

The use of bismuth shields during CT scanning has been shown to reduce anterior surface radiation exposure to the breast and other organs. However, studies reveal that shielding during CT increased image noise and interfered with modern automated tube exposure algorithms, requiring providers to compensate by increasing dose technique during scanning.[114,115] As CT is already performed at a low effective dose (i.e., < 4 mSv), breast shielding may not further reduce the potential biologic impact of radiation.[114] Consistent with the American Association of Physicists in Medicine statement, we do not recommend the use of breast shields but recommend aggressive dose reduction via optimization of patient preparation and scan parameters.[116]

Recently, investigators have studied the impact of manually displacing the mobile portion of breast tissue outside of the field of view during cardiac CT imaging (Fig. 9). This both reduces the dose to breast tissue and reduces photon attenuation during scout and cardiac CT acquisition, resulting in the use of lower tube current during cardiac CT image acquisition and lower overall radiation dose exposure. When combined with an automated tube potential and tube current algorithms, up to a ~33% reduction is achievable in effective radiation reduction through breast displacement in women versus men of a similar body mass index.[117] In a small randomized trial, breast surface dose measured using thermoluminescent dosimetry was reduced 23% with breast displacement versus a 36% reduction by the combination of breast displacement and shielding.[118] Therefore, when possible, displacing mobile breast tissue outside of the field of view is preferable to reduce overall radiation exposure.

6.2. Summary

Although CT imaging has a lower effective dose when compared to nuclear or invasive angiographic procedures, care should be taken to aggressively implement radiation dose reduction techniques in women.

7. Imaging during pregnancy

Imaging using ionizing radiation during pregnancy should only be
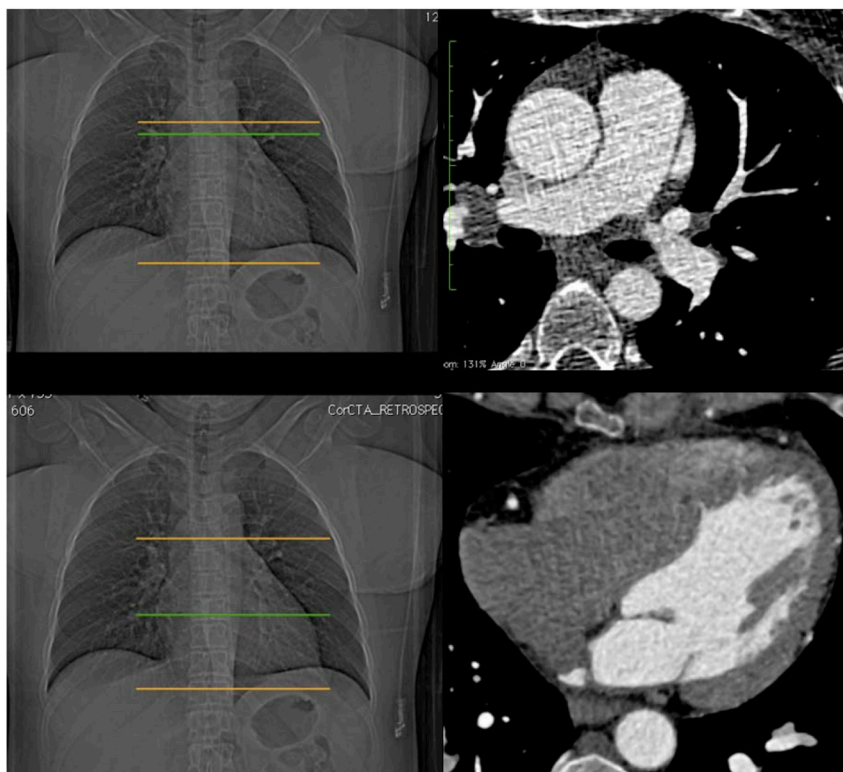
Fig. 9. Illustrative Case of Breast Displacement. Note the top image with the noisy pulmonary artery at the level where the breasts were displaced as compared to the less noisy image of the heart below the displaced breast. Courtesy of Brian Ghoshhajra, MD, Massachusetts General Hospital, Harvard Medical School.

performed if the possible results have the potential to alter management. When considering imaging modalities, it is imperative to identify the lowest radiation modality that will reasonably answer the clinical question. According to an American College of Obstetrics and Gynecology (ACOG), the use of 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.[119] Importantly, the risk from radiation to the fetus is very small for CT imaging of the thorax. The radiation received by the fetus is mainly indirect scatter that originates from within the imaged portion of the patient. Hence, radiation doses to the fetus from chest CT or pulmonary CT angiography to rule out pulmonary embolism are estimated to be approximately 0.02 mGy. CT scans that directly image the fetus have higher doses, for example CTA of the chest, abdomen and pelvis results in 13mGy.[120]

The potential deterministic effect of radiation to the fetus are dependent on the age of gestation and on the level of radiation exposure. At radiation doses of < 50mGy, there is no potential non-stochastic effect independent of gestational age.[120,121] Given that CTA of the thorax is estimated to result in doses of 0.02 mGy, there is negligible risk for non-stochastic fetal harm for CT that is confined to the thorax.

The estimation of stochastic risk is much more difficult due to the challenge in obtaining meaningful data. There are several risk models, all of which lack proper evidence in the low radiation area. Stochastic risk theories generally assume a linear no-threshold model, and hence a test with 0 radiation, would be considered the safest. The American College of Radiology (ACR) and the Radiological Society of North America formed a Joint Task Force on radiation protection (Image Wisely) which lists the stochastic radiation risk to the fetus based on a low, intermediate and high-risk model. According to these models, the incremental risk of cancer from a fetal radiation dose of 10 mGy ranges from 1 in 4545 in the high-risk model to 1 in 1667 in the low risk model (see also www.imagewisely.org).

The ACR practice parameter for imaging pregnant or potentially pregnant women recommends establishing multidisciplinary guidelines

to reduce the potential exposure of fetus or mother by limiting sequential imaging and by utilizing alternative radiation-free test when reasonable and available.[121] Facilities should have policies and procedures in place regulating imaging examinations that involve ionizing radiation in women of child-bearing age.[122] However, if visualization of the coronary arteries is deemed medically necessary, the options are limited. While cardiac MR angiography is radiation-free, it is not widely available. Invasive cardiac catheterization is an alternative strategy but may pose higher procedural risk. Thus, while the widely available non-invasive CTA may be suboptimal due to the radiation exposure, it may be the most viable option for imaging pregnant or potentially pregnant women. Care should be taken to ensure that the CT parameters be tailored to the individual patient to minimize the radiation exposure to as low as reasonably achievable without rendering the resulting images non-diagnostic.[122]

The use of iodinated contrast is not contraindicated in pregnant women; however, its use should be limited to cases where the required information cannot be gained without contrast. Iodinated contrast may enter the fetal circulation via the placenta, and it may be detectable in the amniotic fluid, however there is currently no known evidence linking it to teratogenic, mutagenic or other harm to the fetus.[119,123] The ACOG also recommends that breastfeeding may be continued without a pause after iodinated contrast injections as < 1% of iodinated contrast is excreted into the breast milk, and that less than 1% of that may be ultimately absorbed by the gastrointestinal tract of the infant.[119]

8. Future research needs for CT imaging to enhance clinical care of women

Although the evidence with CT is robust, there are areas of deficiency that could benefit from a greater depth of detail to improve diagnosis and care of women, including enrollment of diverse subgroups with diabetes, hypertension, as well as across racial and ethnic female

Table 1
Clinical indications for CT imaging in women.

Eligible Women	Clinical Recommendation
Evaluation of ASCVD Risk in Asymptomatic Women	• CAC is effective for risk stratification of asymptomatic women with an ASCVD risk score from 5 to 20%. • CAC is effective for risk stratification of asymptomatic women whose ASCVD risk score is discordant with their risk factor profile. • CAC is effective for risk stratification of asymptomatic women with evidence of BAC on mammography.
Suspected CAD Presenting with Stable Chest Pain (or Equivalent) Symptoms to the Outpatient Clinic	• Coronary CTA is effective as initial diagnostic test for symptomatic women with suspected CAD.
Suspected CAD Following an Initial Diagnostic Evaluation with Stress Testing	• CAC Scanning is effective for risk stratification of symptomatic women prior to or immediately following an index stress test to allow for an integrated interpretation of CAC with stress test findings. • CTA is effective as a second-line procedure for risk stratification of women following an indeterminate or intermediate risk stress test. • CTA is effective as a second-line procedure for risk stratification of women with persistent chest pain (or equivalent) symptoms following a negative stress test.
Suspected CAD Presenting with Acute Chest Pain (or Equivalent) Symptoms to the Emergency Department	• CTA is effective as initial diagnostic test for low-intermediate risk women following an initial non-ischemic ECG and negative troponin.

subgroups of the population. The development of female-specific evaluation algorithms should be developed and tested in order to reduce sizeable delays in healthcare seeking and referral patterns which are often protracted in women.[124] Additional comparative effectiveness trials enrolling larger samples of women or women only trials are needed. Generally, only one-quarter of randomized trials include women and more heterogeneous samples of women are required for more robust analysis of clinical endpoints. Imaging provides the possibility to explore a greater depth of detail with regards to atherosclerosis and the explorations with regards to screening of breast and coronary artery calcification can prove fruitful with regards to the development of ASCVD screening. Current ASCVD risk scores imprecisely categorize prognosis and integrative predictive models with CAC should be explored to prove detection of at-risk women.

Strategy trials are needed to develop preventive and anti-ischemic care algorithms for nonobstructive CAD as well as for diverse evaluation of women presenting with chest pain, notably for those with persistent symptoms or for those with indeterminate stress test findings. As these areas disproportionately impact women, enrollment should be high and uniquely tailored to the needs of our female patients. Data suggests that a variable pathobiology may exist between women and men with regards to the atherosclerotic features associated with acute coronary events.[13] Additional data is required in order to more clearly define sex differences in atherogenesis, including variable changes across the age groups of adult and elderly women.

9. Summary statement

The development of highly accurate and effective CVD imaging strategies for the evaluation of women is a primary goal of this expert consensus document from the SCCT. For asymptomatic women, detection of any CAC that reclassifies patients with a 10-year CVD risk of > 7.5% may effectively identify women who may benefit from pharmacologic therapy. For symptomatic women, there is abundant evidence, from large observational registries and randomized trials, that CT imaging is an effective procedure for evaluation of CAD. CTA identifies nonobstructive atherosclerosis, which would otherwise not be detected by conventional stress testing, and allows for improvement in the initiation of preventive therapy. Moreover, CTA has superior risk stratification when compared to stress testing in symptomatic women with stable chest pain (or equivalent) symptoms. A diagnostic strategy supplemented by early CTA in the evaluation of low risk chest pain in the ED is effective for women and markedly reduces LOS. Radiation

dose reduction strategies should be applied in all women undergoing CT imaging. Effective and appropriate use of CT imaging can provide the means for improved detection of at-risk women and thereby focus preventive management resulting in long-term risk reduction and improved clinical outcomes (see Table 1).

Disclosure

First Name	Last Name	Designation	Relevant Relationships
Suhny	Abbara	MD, FSCCT	Royalties: Amirsys/Elsevier
Stephan	Achenbach	MD, FSCCT	
Daniel	Berman	MD, FSCCT	Grant/Research: HeartFlow; Consultant for GE; Royalties: Cedars-Sinai Medical Center
Ron	Blankstein	MD, FSCCT	Grant/Research: Amgen Inc, Gilead Inc.; Consultant: Amgen Inc, Astellas Inc, Ekos Inc.
Renee	Bullock-Palmer	MD, FSCCT	
Patricia	Carrascosa	MD, PhD, FSCCT	
Marcus	Chen	MD	Institutional research agreement between NIH/NHLBI and Canon Medical
Kavitha	Chinnaiyan	MD, FSCCT	Institutional support from Heartflow
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Gudrun	Feuchtner	MD	
Harvey	Hecht	MD, FSCCT	Arineta scientific advisory board
Sang-Eun	Lee	MD	
Jonathon	Leipsic	MD, FSCCT	Grant/Research: GE; Consultant, Stocks & Stock Options: Circle CVI, HeartFlow; Speakers Bureau: GE
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Leslee	Shaw	PhD, FSCCT	
Quynh	Truong	MD, MPH, FSCCT	Grant/Research: Ziosoft; Royalties: UpToDate
Todd	Villines	MD, FSCCT	
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Lilia M.	Sierra Galan	MD, FSCCT	

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Renee																	No	No
Patricia							no	No	no	No	no	No	No		Institutional research agreement between NIH/NHLBI and Canon Medical	No	No	No
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Sang-Eun										No		No
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Aloha		no		na	no	no	no	No		No		No
Francesca		No						No		No		Yes
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Sarah												No	
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2018.10.019.

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