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Imaging and Biomarkers for Subclinical Atherosclerosis in Women

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ABSTRACT

Subclinical atherosclerosis in women remains a silent yet significant contributor to cardiovascular morbidity and mortality. Traditional risk scores often underestimate cardiovascular risk in women, particularly in younger, premenopausal, and autoimmune-prone populations. This diagnostic gap is compounded by sex-specific differences in disease presentation, hormonal influences, and underutilization of imaging modalities such as coronary artery calcium scoring and carotid intima-media thickness, breast arterial calcification, cardiac computed tomography (CT) angiography. Moreover, pregnancy-related complications such as preeclampsia and gestational diabetes are not adequately integrated into current risk models, despite their long-term vascular implications. Given the multifactorial nature of atherosclerosis, no single biomarker or imaging test offers sufficient specificity to guide prognosis or treatment. Instead, a combined approach using non-invasive imaging and novel biomarkers – such as high-sensitivity C-reactive protein, lipoprotein(a), apolipoprotein B, myeloperoxidase, and emerging candidates such as suPAR, microRNAs, and growth differentiation factor-15 – provides a more comprehensive assessment of vascular health. These tools capture both structural and inflammatory aspects of disease, enabling earlier detection and more personalized prevention strategies. Future directions emphasize the development of sex-specific diagnostic algorithms that integrate advanced imaging (e.g., positron emission tomography/magnetic resonance imaging, coronary CT angiography) with multi-biomarker panels. Machine learning models that combine clinical, biochemical, and imaging data are showing promise in refining cardiovascular risk prediction. In addition, research into metabolomics and proteomics is expanding the biomarker landscape, offering new insights into disease mechanisms and therapeutic targets. A gender-sensitive, integrated approach is essential to improve early detection, risk stratification, and outcomes in women with subclinical atherosclerosis. This paradigm shift will help close longstanding gaps in cardiovascular care and support more effective, individualized prevention strategies.

Keywords: Biomarkers, Cardiovascular risk, Imaging, Subclinical atherosclerosis, Women

INTRODUCTION

Subclinical atherosclerosis refers to the early, asymptomatic stages of arterial plaque buildup that precede the onset of overt cardiovascular disease (CVD).^[1] It serves as an early marker of the overall atherosclerotic burden. It is a significant and underdiagnosed contributor to cardiovascular morbidity in women. This burden is particularly acute in India and other South Asian populations, where CVD is rising rapidly, and traditional risk stratification tools often fail to capture the unique pathophysiological profiles of female patients.^[2-4] Despite the high prevalence of metabolic syndrome, diabetes, and hypertension in South Asian women, conventional models such as the Framingham risk score frequently underestimate their cardiovascular risk, and many

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studies stated that traditional risk models underestimate cardiovascular risk in South Asians.^[5,6]

Women in South Asian regions face a distinct set of sex-specific risk factors that further elevate their vulnerability to subclinical atherosclerosis. These include premature menopause, which accelerates vascular ageing due to estrogen deficiency, pregnancy-related complications such as preeclampsia, gestational diabetes, and intrauterine growth restriction, which are linked to long-term endothelial dysfunction. Autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis are more prevalent in women and contribute to chronic vascular inflammation.^[7]

These factors are rarely integrated into routine cardiovascular screening in women, leaving a diagnostic gap that delays early intervention. Therefore, there is an urgent need to adopt a gender-sensitive framework that incorporates advanced imaging and biomarker profiling to detect subclinical atherosclerosis early, especially in high-risk populations across South Asia. Such an approach can enable timely lifestyle modifications and targeted therapies, ultimately improving cardiovascular outcomes for women. Gaining insight into this condition is crucial, as early detection and intervention can significantly reduce the risk of future cardiovascular complications and mortality. Early identification through advanced imaging and biomarker profiling offers a promising avenue for prevention and personalized care.

UNDERSTANDING SUBCLINICAL ATHEROSCLEROSIS

Definition

Atherosclerotic changes in the arterial wall without clinical manifestations such as angina, stroke, or chronic limb ischemia.

Pathophysiology

To date, there is no rigid pathological definition of subclinical atherosclerosis. Based on the presence or absence of ischemic symptoms, atherosclerosis can be defined at the pathological level by lesions that produce no inducible ischemic symptoms, regardless of their histological morphology. The earliest lesion of atherosclerosis is pathological intimal thickening. All lipid-containing lesions are termed plaques.

Specifically, lesions with subclinical atherosclerosis can be classified into 3 categories:^[1]

1. Non-ruptured plaques without severe stenosis (<50%) that may encompass multiple morphological types, pathological intimal thickening (PIT), and fibroatheromas

2. Thrombus formation following plaque rupture, plaque erosion, or calcified nodule that results in no ischemic symptoms but heals and results in luminal narrowing of <50%
3. Lesions with 50–99% stenosis and chronic total occlusion due to progressive atherosclerosis without causing any clinical symptoms.

Gender differences

Though studies^[8] show that men tend to have a higher prevalence of coronary plaque compared to women, especially non-calcified and vulnerable plaques, Women may exhibit slower plaque progression but are more prone to microvascular disease and plaque erosion.

Imaging modalities

Imaging plays a vital role in detecting subclinical atherosclerosis, especially in women, where traditional risk scores may underestimate cardiovascular risk.

The advent of non-invasive imaging techniques has enabled the early detection of atherosclerosis in asymptomatic individuals. Carotid and peripheral vessel ultrasound was the initial method employed, and over time, it has been complemented by more advanced modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) [Table 1].

Carotid artery ultrasound

It is non-invasive and widely accessible, measures intima-media thickness (IMT), and detects plaque presence. IMT > 0.9 mm is associated with increased CVD risk. The carotid intimal-media thickness (CIMT) can be measured both with ultrasound and with MRI, with excellent intra- and inter-observer variability.^[9] In a meta-analysis of 14 studies involving 45,828 asymptomatic subjects undergoing a single measurement of CIMT and then followed for 11 years, CIMT was associated with the risk of the first myocardial infarction or first stroke.^[9]

Dayanand *et al.*^[10] demonstrated that women with polycystic ovary syndrome (PCOS) exhibit significantly higher CIMT (≥ 0.57 mm) compared to age- and weight-matched controls. This evidence supports integrating CIMT measurement into standard PCOS care. This proactive approach could play a pivotal role in mitigating long-term cardiovascular risks in this high-risk population, like women with PCOS.

Studies focused on South Asian adults, including many women, found that psychosocial stress, anxiety, and anger significantly correlate with increased CIMT, which is a marker of subclinical atherosclerosis, and highlighted the need for culturally tailored early screening.^[11,12]

Coronary artery calcium (CAC) scoring

CAC is a well-established marker of subclinical atherosclerosis, often present in the coronary arteries long before clinically significant stenosis develops. Advances in CT technology in recent years have enabled the acquisition of high-resolution images free from motion artifacts, allowing for more accurate quantification of CAC. It is performed through non-contrast CT, and it quantifies calcified plaque burden using the Agatston score.

In a study from Shaw *et al.*,^[13] Sex differences in calcified plaque and long-term cardiovascular mortality were observed. They found that for women, 60%, 25%, 9%, and 5%, respectively, had a CAC score of 0, 1–100, 101–399, and >400. Among those with detectable CAC, the relative hazard for CVD mortality was 1.3-fold higher for women as compared to men.^[13] In the same study, higher CVD mortality was reported for women as compared to men with two or more calcified vessels.

CAC scoring holds unique predictive value in Indian and South Asian women, who often present with lower absolute scores yet experience disproportionately high cardiovascular event rates, especially post-menopause.

South Asian women show a delayed but accelerated rise in CAC scores, particularly after age 50, as highlighted in Shaw *et al.*^[13] and subsequent Mediators of Atherosclerosis in South Asians Living in America (MASALA) and Multi-Ethnic Study of Atherosclerosis (MESA) studies.^[14,15]

Menopause and CAC progression in women

During menopause, estrogen levels decline, leading to increased low-density lipoprotein-cholesterol (LDL-C), reduced vascular elasticity, and heightened inflammatory response. These changes accelerate atherosclerotic plaque formation, including calcification.

Premenopausal women typically have very low or zero CAC scores, even with risk factors.

However, after menopause, CAC scores rise significantly, especially in women with risk factors like hypertension, diabetes, and metabolic syndrome. Studies show that postmenopausal women with detectable CAC have a higher relative risk of cardiovascular events than men with similar scores. Thus, CAC screening becomes more valuable in postmenopausal women, especially those with intermediate risk.

As menopause is a critical inflection point, Shaw *et al.* emphasized that postmenopausal women experience a sharp increase in CAC progression, likely due to hormonal changes, endothelial dysfunction, and metabolic shifts.^[13]

A study by Chandran *et al.*^[16] emphasized CAC's role as a sensitive marker for cardiovascular risk even in asymptomatic

individuals. This study supports the growing consensus that CAC scoring is a valuable tool for personalized cardiovascular risk assessment in women, particularly in South Asian populations where traditional risk models may underestimate true risk.

“Is it Time to Redefine Criteria for Coronary Artery Calcification Significance for South-Asian Women?” An editorial by Patnaik^[17] highlighted the limitations of applying generalized CAC scoring thresholds to South Asian women, a group known to have disproportionately high cardiovascular event rates despite lower absolute CAC scores. The editorial emphasized that menopause marks a critical shift in cardiovascular risk, with accelerated CAC progression likely driven by hormonal and metabolic changes.

Clinical implications of CAC

CAC score >0 in South Asian women should not be dismissed as low risk—even scores of 1–10 may carry significant predictive value.

Menopause should trigger CAC screening, especially in women with a family history or metabolic syndrome.

CAC can guide intensification of statin therapy, lifestyle modification, and biomarker monitoring even in women with borderline traditional risk scores.

Cardiac CT angiography (CCTA)

Zero CAC score in postmenopausal women is reassuring, but non-calcified plaque may still be present, suggesting the need for complementary imaging like CCTA. It provides a non-invasive, high-resolution view of both calcified and non-calcified plaques, helping detect disease that other tests might overlook.

It detects plaque morphology, stenosis severity, and vessel remodeling, and also helps guide early preventive therapy (e.g., statins, lifestyle changes).^[18] However, it is widely used as a diagnostic test for low-to-intermediate risk, stable, and symptomatic women.

Breast arterial calcification (BAC)

It refers to medial calcification of breast arteries visible on mammograms. Though traditionally considered incidental, BAC is now recognized as a marker of subclinical atherosclerosis, especially in women. It correlates with coronary artery disease (CAD), stroke, and cardiovascular mortality, particularly in postmenopausal women. In an Indian study, Gopalan *et al.*,^[19] BAC, detected through mammography, has been observed in approximately 25% of Indian women over the age of 40 years. Emerging evidence suggests a strong correlation between BAC and cardiovascular risk factors, positioning it as a promising, low-cost tool for cardiovascular screening during routine breast cancer evaluation [Table 1].

Table 1: Summary of various imaging modalities for subclinical atherosclerosis in women.

Imaging modality	Advantages	Limitations
CIMT	<ol style="list-style-type: none"> 1. Non-invasive and widely accessible 2. Detects early vascular ageing 3. Applicable in low-resource settings 	<ol style="list-style-type: none"> 1. Operator dependent 2. Limited specificity for plaque composition 3. May not reflect coronary artery status
CAC scoring	<ol style="list-style-type: none"> 1. Quantifies calcified plaque burden 2. Strong predictor of CV events Useful in postmenopausal women	<ol style="list-style-type: none"> 1. Standardised scoring (Agatston)- Underestimates risk in women with non-calcified plaques 2. Less predictive in premenopausal women 3. No information on plaque morphology
CCTA	<ol style="list-style-type: none"> 1. Detects both calcified and non-calcified plaques 2. Assesses stenosis severity and vessel remodelling 3. Valuable in symptomatic women with zero CAC 	<ol style="list-style-type: none"> 1. Higher radiation exposure 2. Requires contrast administration 3. Costly and less accessible in low-resource settings
BAC	<ol style="list-style-type: none"> 1. Cost effective and non-invasive, and accessible via routine mammography ideal for population-level risk stratification 2. Particularly valuable in postmenopausal Indian women 3. Correlates with cardiovascular risk factors, especially relevant in Indian women over 40 	<ol style="list-style-type: none"> 1. Limited validation across populations 2. Not yet standard in cardiovascular screening 3. Detects medial calcification, not atherosclerotic plaque directly
PET/MRI	<ol style="list-style-type: none"> 1. Detects arterial inflammation and metabolic activity 2. Can identify disease before plaque formation 3. Promising for autoimmune-prone populations 	<ol style="list-style-type: none"> 1. Expensive and limited availability 2. Primarily used in research settings 3. Requires specialised expertise

BAC: Breast arterial calcification, CAC: Coronary artery calcium, CCTA: Cardiac computed tomography angiography, CIMT: Carotid intimal-media thickness, CT: Computed tomography, PET: Positron emission tomography, MRI: Magnetic resonance imaging, CAC: Coronary artery calcium, CV: Cardiovascular

Role of artificial intelligence (AI) in BAC detection

AI algorithms can automatically detect, quantify, and classify BAC on routine mammograms which enable opportunistic cardiovascular screening without additional imaging or radiation.^[20] AI improves accuracy, consistency, and scalability, especially in resource-limited settings [Table 2].

AI-based BAC screening during mammography is emerging as a powerful tool for detecting cardiovascular risk in women, with a notable Indian study by Gopalan *et al.*^[19] highlighting its feasibility and impact.

MRI and positron emission tomography (PET) imaging

MRI and PET imaging offer advanced detection of subclinical atherosclerosis. MRI provides detailed vessel wall imaging without radiation but is limited by cost, scan time, and sensitivity to inflammation. PET detects metabolic activity and inflammation, identifying early disease even in plaque-free areas. Combined PET/MRI enhances early detection and risk assessment. Studies show PET/MRI can detect arterial inflammation in plaque-free regions, suggesting it may identify atherosclerosis at its earliest stages.^[21,22]

AI APPLICATIONS IN IMAGING FOR SUBCLINICAL ATHEROSCLEROSIS

AI integrates data from CTA, PET, and MRI with clinical and genomic data to build personalized risk profiles, which is particularly valuable for women, whose atherosclerosis may

present with diffuse, non-obstructive patterns. AI can help overcome gender bias in imaging interpretation, especially where atypical presentations are common.

The AI-CAC model demonstrated strong predictive power for subclinical atherosclerosis, even in low-risk populations.^[23-25]

Biomarkers in detection and risk stratification

Subclinical atherosclerosis in women is influenced by a diverse array of biomarkers that reflect lipid metabolism, inflammation, endothelial dysfunction, oxidative stress, and cardiac strain. These biomarkers help detect early vascular changes before symptoms appear, stratify risk in asymptomatic individuals, especially when traditional scores fall short [Table 2].

Inflammatory markers

Inflammation plays a central role in the development and progression of subclinical atherosclerosis, and in women, this process is often influenced by hormonal changes, immune responses, and metabolic factors.^[26]

High-sensitivity C-reactive protein (hs-CRP) is a marker of systemic inflammation. Elevated hs-CRP is more predictive of cardiovascular events in women than in men, especially during postmenopause. It helps identify at-risk women even with normal cholesterol levels.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine linked to endothelial dysfunction and plaque vulnerability. In women,

Table 2: Summary of biomarkers for subclinical atherosclerosis in women.

Biomarkers	Clinical utility	Limitations
Inflammatory markers		
Hs-CRP, IL-6, TNF- α , CRP	<ul style="list-style-type: none"> • CRP >3 mg/L (high risk)- Predictive in postmenopausal women, even with normal lipids • IL-6 >5 pg/mL- Linked to plaque vulnerability, reflects hormonal and age-related shifts • TNF-α >8.1 pg/mL- Elevated in autoimmune-prone women • Indicates plaque instability. 	<ul style="list-style-type: none"> • Non-specific, influenced by infections and chronic conditions • IL-6 has a short half-life • Costly and variable assays • Low specificity, is affected by systemic inflammation.
Lipid markers		
LDL-C, HDL-C, Lp (a), ApoB, Oxidised LDL, non-HDL-C	<ul style="list-style-type: none"> • Lp (a) lipid metabolism >50 mg/dL, genetically driven, not diet-dependent • ApoB lipid metabolism >90 mg/dL, Better predictor than LDL-C, Oxidised LDL lipid metabolism: Elevated levels (no fixed cutoff)- Indicates endothelial dysfunction, Elevated in autoimmune conditions • Non-HDL-C >130 mg/dL captures all atherogenic particles, a Strong predictor in women. 	<ul style="list-style-type: none"> • Limited treatment, ethnic variability • Not routinely measured • Costlier than standard lipid panels. • Not standardized, Limited clinical use • Influenced by triglycerides, Less specific than ApoB.
Vascular injury biomarkers		
sICAM-1/VCAM-1, Endothelin-1, MPO/ Lp-PLA2, Albumin/ Creatinine Ratio, Homocysteine, hs-Troponin I/T, BNP/NT-proBNP	<ul style="list-style-type: none"> • Elevated levels of sICAM-1/VCAM-1 reflect early endothelial dysfunction • Endothelin-1 >1.0 pg/mL- Indicates vascular remodelling and stiffness • hs-Troponin I/T >0.04 ng/mL- Detects silent myocardial injury and is Useful in microvascular disease • BNP/NT-proBNP, BNP >100 pg/mL, NT-proBNP >125 pg/mL reflect cardiac wall strain, predict vascular stiffness. 	<ul style="list-style-type: none"> • Not widely available, mostly used in research • Limited clinical use • Affected by stress and hormones • May rise in non-ischemic conditions • Requires serial testing • Influenced by age, renal function, and obesity.
<p>Hs-CRP: High-sensitivity C-reactive protein, BNP: B-type natriuretic peptide, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, LDL-C: Low density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, IL-6: Interleukin-6, TNF-α: Tumour necrosis factor-alpha, sICAM: Soluble intercellular adhesion molecule-1, VCAM-1: Vascular cell adhesion molecule-1, ApoB: Apolipoprotein B, hs-Troponin: High-sensitivity troponin, Lp(a): Lipoprotein(a), LP-PLA2: Lipoprotein-Associated Phospholipase A2,</p>		

IL-6 levels rise with age and hormonal shifts, contributing to vascular inflammation. Tumor necrosis factor-alpha (TNF- α) promotes vascular inflammation and plaque instability, and may be elevated in autoimmune conditions, such as lupus or rheumatoid arthritis, which are more prevalent in women.

Lipid and lipoprotein markers

Women often exhibit unique lipid profiles that influence cardiovascular risk, especially during hormonal transitions such as menopause. Key biomarkers include Lipoprotein(a) [Lp(a)], a genetically driven risk factor particularly significant in women with a family history of early heart disease, and apolipoprotein B, which reflects the total number of atherogenic particles and offers better risk prediction than LDL-C alone.^[27] Oxidized LDL is linked to endothelial dysfunction and is often elevated in women with autoimmune conditions. The lipid accumulation product, combining waist circumference and triglycerides, correlates with metabolic risk in menopausal women. Finally, non-high-density lipoprotein cholesterol (HDL-C), encompassing all atherogenic lipoproteins, is a strong

Screen for Lp(a) once in a lifetime, especially if:

- Family history of premature CAD
- Personal history of early or unexplained ASCVD
- Intermediate risk with normal LDL-C
- Integrate Lp(a) into risk calculators for more accurate stratification in Indian women
- Educate clinicians and patients about its significance, especially in South Asian populations.

Figure 1: Clinical recommendations for lipoprotein(a) in Indian women. (CAD: Coronary Artery Disease, ASCVD: Atherosclerotic Cardiovascular Disease, LDL-C: Low Density Lipoprotein-Cholesterol, Lp(a): Lipoprotein (a))

- Begin CAC screening between the ages of 45–50 in South Asian women, particularly if postmenopausal.
- Apply sex-specific CAC percentiles for more accurate interpretation.
- Combine CAC with biomarkers such as hs-CRP, Lp(a), and ApoB/ApoA1 for a comprehensive cardiovascular risk profile

Figure 2: Recommendations combining imaging and biomarker. (CAC: Coronary artery calcium, hs-CRP: high sensitivity C-reactive protein, Lp(a): Lipoprotein (a), ApoA1/B: Apolipoprotein B/ Apolipoprotein A1)

predictor of subclinical disease, especially in women with elevated triglycerides. These atherogenic indices are found to correlate with CIMT and, considering the cost factor for some important biomarkers for atherosclerosis and imaging techniques, atherogenic indices can be considered as surrogate biomarkers of subclinical atherosclerosis and cost-effective predictors of CVD risk.^[28,29]

Lp(a) is an LDL-like particle with an added apolipoprotein(a) component. It promotes atherogenesis through pro-inflammatory, pro-thrombotic, and pro-calcific mechanisms. Lp(a) levels are 90% genetically determined and remain relatively stable throughout life. In Indian women, Lp(a) may amplify ASCVD risk even in the absence of traditional risk factors such as diabetes or hypertension. It contributes to non-obstructive and diffuse atherosclerosis, which is more common in women and often missed by standard angiography. South Asians, including Indians, have among the highest global median Lp(a) levels, often exceeding 30 mg/dL. Studies show that 25–30% of South Asians have elevated Lp(a) (>50 mg/dL), a threshold associated with increased atherosclerotic cardiovascular disease (ASCVD) risk.^[30,31] Indian women, particularly postmenopausal, exhibit higher Lp(a) levels than men, possibly due to hormonal influences and genetic predisposition.^[29] Its genetic basis, resistance to lifestyle modification, and under-recognition in clinical practice make it a critical biomarker for early screening in this population.

Apo-B levels strongly predict ASCVD risk, outperforming LDL-C in certain populations, particularly important in diabetic and dyslipidemic women, where traditional lipid measures may underestimate risk.^[32]

hs-CRP, apolipoprotein B (ApoB), Lp(a), non-HDL-C, and oxidized LDL should be used as routine biomarkers for early CAD detection and risk stratification in women, especially those with metabolic syndrome or diabetic profiles.^[33]

Other markers

A range of non-lipid biomarkers, including markers of endothelial dysfunction (soluble intercellular adhesion molecule-1, vascular cell adhesion molecule-1, endothelin-1), inflammation (myeloperoxidase [MPO], Lipoprotein-associated phospholipase A2 (Lp-PLA2), and metabolic stress (albumin-to-creatinine ratio, homocysteine) may help detect subclinical atherosclerosis, especially in women. Cardiac stress markers such as high-sensitivity troponins and B-type natriuretic peptide (BNP) also reveal silent myocardial injury and vascular stiffness, offering valuable insight into early cardiovascular risk even in asymptomatic individuals.^[34,35]

Several novel biomarkers are showing promise in detecting subclinical atherosclerosis before structural changes appear.

These include inflammatory markers such as Lp-PLA2 and suPAR, regulatory microRNAs, and vascular calcification markers such as osteoprotegerin. Others, such as growth differentiation factor-15, endothelial progenitor cells, and trimethylamine N-oxide, reflect oxidative stress, endothelial repair, and the influence of the gut microbiome. All together, these biomarkers provide a more nuanced view of cardiovascular risk, especially in women, and may enhance traditional risk scores^[36,37] though their clinical integration is still under investigation.

Combining imaging and biomarkers to detect subclinical atherosclerosis:

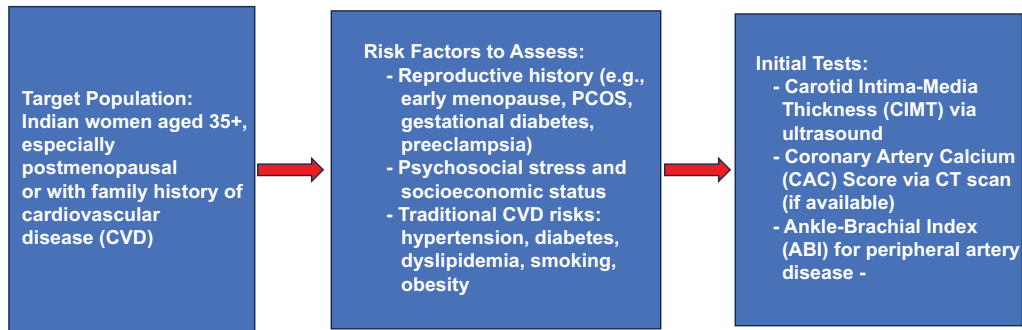
Combining imaging techniques such as CAC scoring, CIMT, and CCTA with biomarkers such as hs-CRP, lipoprotein(a), ApoB, and MPO offers a comprehensive approach to detecting subclinical atherosclerosis in women.

Table 3: Recent Indian studies on imaging modalities for subclinical atherosclerosis.

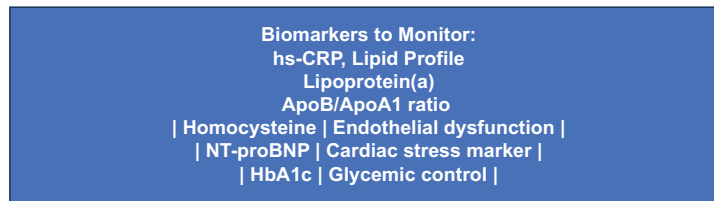
Study	Key points
Chandran <i>et al.</i> ^[16] (2025)	<ol style="list-style-type: none"> 1. CAC scores rise significantly with age, especially post-menopause, highlighting vascular aging in coronary risk. 2. Diabetic women show markedly higher CAC scores, confirming diabetes as a major driver of subclinical atherosclerosis. 3. Hypertension, dyslipidemia, and metabolic syndrome are linked to elevated CAC scores, even in women with low/borderline traditional risk. 4. Many women with CAC > 0 were symptom-free, showing CAC scoring reveals hidden CV risk missed by standard assessments.
Patnaik <i>et al.</i> ^[17] (2025)	<ol style="list-style-type: none"> 1. High risk South Asian women often have lower CAC scores but higher coronary event rates compared to other groups. 2. Menopause accelerates CAC progression due to hormonal and metabolic shifts, increasing CV risk. 3. Standard CAC cutoffs may miss high-risk South Asian women, especially those with diabetes or strong family history. 4. Need for ethnicity- and sex -specific CAC percentiles and earlier screening in postmenopausal South Asian women.
Gopalan <i>et al.</i> ^[19] (2025)	<ol style="list-style-type: none"> 1. High prevalence of BAC in Indian women over 50, particularly with diabetes and hypertension. 2. AI-based BAC detection strongly correlated with CAC scores, supporting BAC as a surrogate marker. 3. Study emphasised incorporating BAC screening into routine mammography workflows for early CV risk identification.

CAC: Coronary artery calcium, BAC: Breast arterial calcification, CV: Cardiovascular

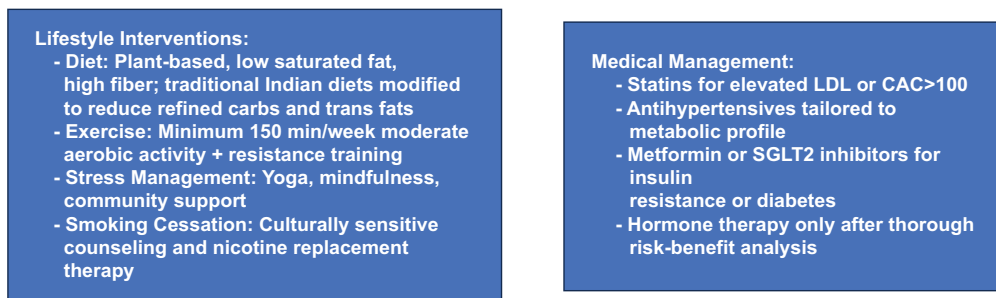
Step 1: Risk stratification and initial screening



Step 2: Biomarker-guided follow-up.



Step 3: Aggressive lifestyle and risk factor modification.



Step 4: Monitoring and reassessment

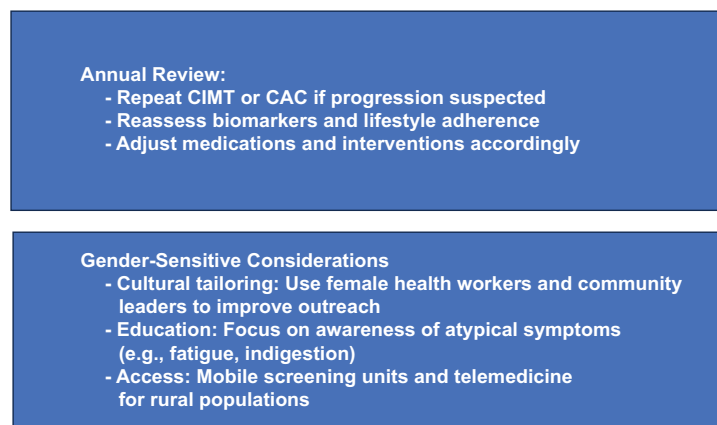


Figure 3: A gender-sensitive screening algorithm tailored for Indian women with biomarker-guided follow-up and aggressive lifestyle/risk factor modification. Note: Frequency: Every 6–12 months, depending on baseline risk and progression. (PCOS: Polycystic ovarian syndrome, hs-CRP: high sensitivity protein, ApoB/ApoA1: Apolipoprotein B/ApolipoproteinA1, NT-proBNP: N-Terminal pro B-type natriuretic peptide, HBA1C: Hemoglobin A1c, LDL: Low density lipoprotein, CAC: Coronary artery calcium, SGLT :Sodium glucose Co-transporter). Step 1: Risk Stratification and Initial Screening. Step 2: Biomarker-Guided Followup. Step 3: Aggressive lifestyle and risk factor modification. Step 4: Monitoring and Reassessment

This integrated strategy enhances early risk identification, especially in postmenopausal and autoimmune-prone individuals, by capturing both structural and inflammatory aspects of disease [Figures 1 and 2].

KEY INDIAN STUDIES, GUIDELINES AND CONSENSUS STATEMENTS:

India does not yet have dedicated national guidelines specifically for subclinical atherosclerosis in women, but recent consensus statements and expert reviews offer gender-sensitive recommendations within broader cardiovascular risk frameworks [Table 3].

Lipid association of India – 2024 guidelines

Recommends lifetime Lp(a) screening in women with family history or premature CAD.

Advocates for CAC scoring in intermediate-risk women, especially postmenopausal.^[38,39]

Apollo subclinical coronary atherosclerosis project – 2023 findings

- High burden of subclinical atherosclerosis in Indian women, often with low CAC scores but high event rates.
- Supports early imaging-based screening in women aged 40+, especially with metabolic syndrome.^[40]

Indian Journal of CVD in Women – expert reviews which focused on gender-specific CVD patterns recommendations

- Use CIMT and BAC screening opportunistically during routine imaging
- Incorporate AI tools for CAC and BAC detection in women with atypical symptoms
- Stress on lifestyle modification and biomarker-guided follow-up for subclinical disease.^[41]

CHALLENGES AND FUTURE DIRECTIONS

Assessing and managing subclinical atherosclerosis in women are challenging due to sex-specific differences in disease presentation, underestimation of risk by traditional scores, and underuse of imaging tools such as CAC scoring and CIMT. Current guidelines often overlook the impact of hormonal changes, autoimmune diseases, and pregnancy-related complications. To address the gaps, future strategies aim to develop specific diagnostic algorithms [Figure 3] in women that integrate advanced imaging with multi-biomarker panels. Emerging approaches, including machine learning and novel biomarkers from metabolomics and proteomics, hold promise for improving early detection and

personalized cardiovascular prevention in diverse female populations.

CONCLUSION

Subclinical atherosclerosis in women often goes undetected yet significantly contributes to CVD. Due to its complex nature, no single test can reliably assess its severity or guide treatment. Instead, combining biomarkers with noninvasive imaging – such as CAC scoring and CIMT – offers a more accurate prediction of adverse cardiovascular events, particularly in women whose risk is frequently underestimated. Adopting a gender-sensitive approach is crucial to bridging diagnostic gaps and enhancing clinical outcomes.

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