

## Quantification of Coronary Atherosclerosis in the Pre-Peri Menopausal Female Based on Cardiac CCTA

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### Abstract

**Introduction:** The pre/peri-menopausal female is believed to have minimal risk for coronary atherosclerosis based primarily on inadequate noninvasive techniques. Cardiac Computed Tomography Angiography (CCTA), the most sensitive tool for quantifying coronary atherosclerosis, was performed to quantify subclinical coronary atherosclerosis in this population.

#### Methods:

We conducted a retrospective chart review on 500 females aged 35-60 presenting with chest pain and shortness of breath. These were consecutive admissions in which CCTA was performed from January 2014 to December 2019. The degree of coronary atherosclerosis was quantified based on the percentage of luminal obstruction and the CAD-RADS scoring system.

#### Results:

Analysis showed that 69.4% (347) of patients had no evidence of obstructive coronary atherosclerosis, another 24.6% had less than 50% obstruction, and only 6% had more than 50% obstruction. Each category of stenosis typically had multiple vessels involved. Over 60% of patients were Non-Hispanic White, 20% Hispanic, 8% Non-Hispanic Black and 4% Asian.

#### Conclusions:

This is the first study to quantify subclinical coronary atherosclerosis in the pre/peri-menopausal female, based on coronary angiograms obtained by CCTA. Nearly 70% were without obstructive CAD, while 30% had detectable CAD by CCTA, with only 6% having greater than 50% stenosis. These results suggest primary preventative therapy in women even as late as the 40s or 50s would be expected to significantly prevent the progression of coronary atherosclerosis and its subsequent sequelae.

**Keywords:** coronary artery disease; CCTA; subclinical atherosclerosis; prevention of CAD

### Introduction:

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality in men and women 1. The primary cause of coronary artery disease is atherosclerosis, which develops in the epicardial coronary vessels and is initiated primarily by the accumulation of oxidized low-density lipoprotein cholesterol (LDL-C), leading to plaque formation 2.

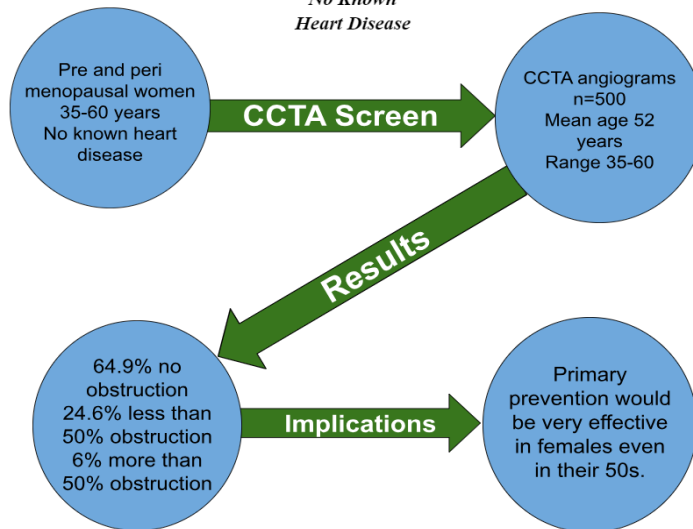
These plaques commence in the vessel wall, expand inward to involve the media, and also outward into the lumen, causing varying degrees of coronary obstruction<sup>3</sup>. Atherosclerosis develops in the first decade of life<sup>4</sup> and progresses gradually over decades without any clinical manifestations, referred to as subclinical atherosclerosis<sup>5</sup>. Myocardial infarction, a common and serious clinical manifestation, is usually due to a thrombus superimposed on a ruptured or eroded plaque occurring in individuals with less than 50% coronary obstruction<sup>6</sup>. Since this degree of coronary obstruction does not significantly impair coronary flow, the formation of a thrombus is due primarily to vessel wall dysfunction induced by atherosclerosis<sup>7</sup>. Myocardial infarction peaks in males in the 6th decade, with a peak incidence at age 58<sup>8</sup>. Clinical manifestations are delayed for about a decade in females, with the peak infarction incidence occurring at age 68<sup>9</sup>.

The delay in the onset of clinical manifestations in females has been recognized for decades and attributed to the essential role of premenopausal hormones in cardiovascular protection<sup>10</sup>. It is assumed these hormones delay the progression of coronary atherosclerosis. However, studies attempting to quantify subclinical coronary atherosclerosis, particularly in females, have been less than adequate<sup>11</sup>. Early studies<sup>12,13</sup> were based on an electrocardiogram performed before and after exercise, which provided less than adequate sensitivity and specificity. Myocardial imaging<sup>14</sup> performed before and after exercise, while more sensitive and specific, is also designed to detect ischemia due to clinically-significant coronary obstruction. Selective coronary angiography<sup>15,16</sup>, the gold standard to visualize the extent of coronary atherosclerosis, was not performed as a routine diagnostic procedure in middle-aged females since it is an invasive procedure, and women were previously not expected to have heart disease at this age. However, all of these techniques, including coronary angiography, are diagnostic techniques designed to detect myocardial ischemia induced by luminal obstruction that is severe enough to reduce coronary blood flow. A sensitive technique to quantify asymptomatic obstructive subclinical coronary atherosclerosis only became available recently<sup>17</sup>. Coronary Computed Tomography Angiography (CCTA) is a noninvasive and safe (low radiation) imaging modality in women that enables accurate detection and quantification of subclinical coronary atherosclerosis<sup>18,19</sup>. Thus, utilizing CCTA, this study was designed to quantify the extent of coronary atherosclerosis in pre- and peri-menopausal females aged 35-60 years without known heart disease.

### Methods:

This study is a retrospective chart review (Figure 1) initiated on January 1, 2014, and completed on December 31, 2019, at the Dignity Health System involving St. Joseph Hospital and Medical Center (SJHMC), Mercy Gilbert Medical Center, and Chandler Regional Medical Center. The study was conducted according to US standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6). Dignity Health research policies and procedures were followed. The protocol and all amendments were approved by the SJHMC Institutional Review Board (IRB). This study poses minimal to no risk to the patients by virtue of its retrospective design. Because of the retrospective nature of this study, no clinician-patient contact was required; therefore, informed consent was waived.

**Figure 1: CCTA Analysis of Pre-peri Menopausal Women with No Known Heart Disease**



### Legend:

CAD is coronary artery disease. Rad is reporting and data system.

Enrollment in the study included females aged 35 to 60 years of age, presenting with atypical chest pain or shortness of breath, no known history of heart disease, and having a CCTA performed. The participants were identified from the electronic medical records of each institution. Basic demographic data such as age, sex, race and ethnicity were collected from the participant's medical records.

Participants underwent cardiovascular assessment including CCTA. The participating sites obtained CCTA images using  $\geq 64$  detector row CT scanners. Image acquisition, image post-processing, and interpretation were performed by certified physicians in accordance with the Society of Cardiovascular Computed Tomography guidelines. CAD was defined as any lesion  $\geq 1$  mm that existed within the coronary lumen or adjacent to the lumen that could be distinguished from surrounding pericardial fat or the artery lumen itself. The coronary plaque was classified as calcified, partially calcified, or non-calcified. The severity of stenosis was graded as follows: 0%, 1–24%, 25–49%, 50–69%, 70–99%, and 100%. Significant coronary obstruction was defined as  $\geq 50\%$  stenosis<sup>20</sup>.

All clinical data, such as the patient's name and date of birth, were assigned a non-identifying study-specific code in Redcap. Redcap is a dedicated database with multi-level security. Only the PI, co-investigators, statisticians, and authorized regulatory agencies have access to the research data. The Investigators are responsible for maintaining database access and overseeing security. At the time of study closure, all patient identifiers were deleted, and only de-identified data were archived in Red Cap. Due to the retrospective nature of this study, no patient adverse events are anticipated as the result of this research, with the exception of a minor risk of loss of confidentiality. These risks will be mitigated per the above, and any breaches of confidentiality will be promptly disclosed. All members involved in the study were trained to follow the

institutional protocols of the GCP guidelines.

The target sample size was 500 patients. The statistical analysis was performed utilizing SPSS version 25.

### Results:

In this study, investigators reviewed 500 women who had consecutively undergone CCTA. A summary of the demographics and baseline data is shown in Table 1. It is as expected all individuals were females. The mean age was  $52.18 \pm 4.41$ , varying from 35 to 60 years of age. Over 60% were White, nearly 20% Hispanic, and 8% Black. The results of the CCTA were striking in that 69.4% (347) were classified as having zero coronary obstruction, with another 24.6% (123) having less than 50% obstruction. Thus, only 6% (30) had 50% or more coronary obstruction. In the 6%, there were ten individuals with two-vessel disease, nine individuals with triple vessel disease, and two individuals with four-vessel disease. There was high correlation between the coronary calcium score and the percentage of luminal obstruction (table 2). The CAD RAD score developed (20) to categorize coronary obstruction observed on CCTA showed an even greater percentage of 94% (471) (table 2) had a score of zero.

Population n=500		Mean Age $52.18 \pm 4$ yrs
		%(n)
<b>Age Distribution (yrs)</b>		
<b>45-50</b>		<b>39.6 (198)</b>
<b>51-55</b>		<b>34.2 (171)</b>
<b>56-60</b>		<b>26.2 (131)</b>
<b>Race</b>		
<b>White</b>		65.6 (328)
<b>Black</b>		8 (40)
<b>Hispanic</b>		19.6 (98)
<b>Other</b>		6.8 (34)
<b>Current Smoker</b>		16.4 (82)
<b>Current Alcohol</b>		29.2 (146)
<b>Hyperlipidemia</b>		21.4 (107)
<b>Hypertension</b>		36.4 (182)
<b>Diabetes</b>		14.8 (74)
<b>Family History of Heart Disease</b>		34.4 (173)

**Table 1:** Baseline Characteristics and Demographics

		%(n)
<b>Coronary Stenosis</b>		
<b>0%</b>		69.4 (347)
<b>&lt;25%</b>		12.4 (62)
<b>25-49%</b>		12.2 (61)
<b>50-75%</b>		4.6 (23)
<b>75-100%</b>		1.4 (7)
<b>Calcium Score</b>		
<b>0</b>		69.8 (349)
<b>1-100</b>		22.4 (112)
<b>101-300</b>		5.4 (27)
<b>301&gt;</b>		2.4 (12)
<b>CAD rad score</b>		
<b>0</b>		94.2 (471)
<b>1</b>		2.0 (10)
<b>2</b>		2.4 (12)
<b>3</b>		1.0 (5)
<b>4</b>		0.4 (2)

**Table 2:** Results of the CCTA Study

### Discussion:

Selective coronary angiograms were obtained by CCTA in 500 females varying in age from 35 to 60 years. No coronary obstruction was observed in 70%, with another 25% having less than 50% obstruction. Based on a literature search, this is the first systematic study using CCTA to quantify the degree of subclinical coronary atherosclerosis in pre-perimenopausal women. The mean age of onset of menopause in American women is 51 years and varies from 45 to 55 years 21. The mean age of the women included in this study was 52 years. This study indicates that the progression of subclinical coronary atherosclerosis is delayed in women prior to menopause. Although the majority of women between the ages of 45-60 years had minimal or no coronary obstruction on CCTA, 30% had evidence of coronary atherosclerosis, of which 6% (1 out of 17) had obstructive disease. The implication being primary prevention initiated in pre-perimenopausal women, even in their 40s or 50s would be expected to be very effective in preventing future cardiac events.

It is well known that atherosclerosis of the coronaries begins in the first decade of life, as determined by autopsies of young soldiers dying in combat 22 and from young individuals killed in various accidents 23,24. The progression of coronary atherosclerosis is slow and gradual, requiring decades to reach the threshold necessary to manifest clinical features such as angina or myocardial infarction 25. This threshold, based on age, usually occurs in the 6th to 7th decade in males or in the 7th or 8th decade in females 26. Ference et al. 27 recognized that the intensity and duration of exposure to plasma LDL-C are critical in determining the rate of development of coronary atherosclerosis and the time required to reach a clinical threshold. To define this threshold, they combined both parameters by multiplying the chronological age

times the plasma LDL-C mg/dL, and the result is referred to in mg-years 27. They observed the minimal threshold to induce clinical manifestations is around 5,000 mg years 27. Our data show the clinical threshold of coronary artery disease is markedly delayed in women in the age group between 35 and 60 years.

Numerous clinical trials have shown CAD is preventable with a consistent 30-40% reduction in mortality and morbidity associated with decreasing the risk of known risk factors such as plasma LDL-C 27–29. The Global Cardiovascular Consortium reported that about 50% of the cardiovascular risk is preventable by decreasing the risk associated with five conventional risk factors 30. Primary prevention of CAD is the desired and most effective approach. Recent evidence, primarily from genetic studies, shows primary prevention initiated early can be 2 to 3-fold more effective. A familial disorder 31 due to a loss of function mutation in the PCSK9 gene was associated with an 80% reduction in cardiac risk. Mendelian analysis shows that a reduction in plasma LDL-C from conception due to a favorable genetic variant is associated with about 54% reduction in CAD risk per mmol (37.8mg/dl) reduction of plasma LDL-C. This is in sharp contrast to the 22% reduction in cardiac events observed per mmol reduction of plasma LDL-C in clinical trials performed over 3 to 5 years 32. These results are in keeping with the observation that every additional 10-year exposure to the same plasma LDL-C doubles the cardiac risk 33.

Due to the limitations of the current standard multi-societal guidelines there has never been a major thrust to initiate primary prevention in the premenopausal period. This study should serve as a catalyst for exploring sex-specific prevention and facilitate the development of tailored early primary prevention strategies. Our data based on CCTA indicate such an initiative, if undertaken with primary prevention in the 40s or even early 50s in females, would be expected to have a much greater effect than in males at this age. The 2018 ACC/AHA Clinical Guidelines only recommend decreasing plasma LDL-C as primary prevention in those at increased risk. The minimum increased risk is defined as having a 7.5% risk for CAD over the next ten years calculated by the pooled cohort equation based on conventional risk factors. Unfortunately, the factors contributing to the 7.5% risk, such as hypertension or diabetes, are present in only a small percentage of women in their 40s (33). These risk factors are age-dependent and more applicable to individuals in their 60s, as discussed by several investigators 33–35. This represents a missed opportunity since the mean plasma LDL-C in a female in her 40s is 121 mg/dL, and in males is 146 mg/dL, which is almost twice the level of plasma LDL-C recommended by the guidelines 33,34,36. The results of this study should be considered in future clinical guidelines to improve preventive management.

It is claimed that about 50% of the predisposition for CAD is genetic 37. It is estimated that about 50% of the American population will experience at least one cardiac event in their lifetime 38. The potential to prevent cardiac events in females aged 35 to 60 years is great and proven efficacious preventive measures are available. The challenge may be selecting those at the highest risk. Risk stratification for early primary prevention of CAD utilizing the recently developed polygenic risk score 39–41 in combination with conventional risk factors could be of some merit

in this female age group. Genetic risk can be measured at any time after birth since it is determined at conception and does not change in one's lifetime 34. Individuals in the top 25% of the polygenic risk score (PRS) have a 1-to-3-fold increased risk of CAD and would benefit from early primary prevention. The high genetic risk group for CAD identified by the PRS has been shown to experience significantly reduced cardiac events in response to favorable lifestyle 41, statin drugs 40, and PCSK9 inhibitors 42.

The positive features of our study include selective coronary angiograms performed by CCTA; individuals were assessed consecutively, a significant sample size of 500, and the study was performed in three different medical centers. Limitations include not having the CCTA angiograms interpreted by a single individual or core laboratory. Secondly, our ethnic and geographic distribution may not be reflective of the country in general, and lastly, all participants had a clinical symptom that brought them to the physician. Would the results be more informative if the CCTA had been performed on asymptomatic women in their 40s and 50s? The latter, while perhaps preferred, is probably not possible in our current healthcare system. Nevertheless, we feel the results, being the first to be performed consecutively using CCTA, have highly significant implications for early primary prevention in the female sex.

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