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ORIGINAL RESEARCH

Age- and Sex-Specific Nomographic CT Quantitative Plaque Data From a Large International Cohort

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ABSTRACT

BACKGROUND With growing adoption of coronary computed tomographic angiography (CTA), there is increasing evidence for and interest in the prognostic importance of atherosclerotic plaque volume. Manual tools for plaque segmentation are cumbersome, and their routine implementation in clinical practice is limited.

OBJECTIVES The aim of this study was to develop nomographic quantitative plaque values from a large consecutive multicenter cohort using coronary CTA.

METHODS Quantitative assessment of total atherosclerotic plaque and plaque subtype volumes was performed in patients undergoing clinically indicated coronary CTA, using an Artificial Intelligence-Enabled Quantitative Coronary Plaque Analysis tool.

RESULTS A total of 11,808 patients were included in the analysis; their mean age was 62.7 ± 12.2 years, and 5,423 (45.9%) were women. The median total plaque volume was 223 mm^3 (IQR: 29-614 mm^3) and was significantly higher in male participants (360 mm^3; IQR: 78-805 mm^3) compared with female participants (108 mm^3; IQR: 10-388 mm^3) ($P < 0.0001$). Total plaque increased with age in both male and female patients. Younger patients exhibited a higher prevalence of noncalcified plaque. The distribution of total plaque volume and its components was reported in every decile by age group and sex.

CONCLUSIONS The authors developed pragmatic age- and sex-stratified percentile nomograms for atherosclerotic plaque measures using findings from coronary CTA. The impact of age and sex on total plaque and its components should be considered in the risk-benefit analysis when treating patients. Artificial Intelligence-Enabled Quantitative Coronary Plaque Analysis work flows could provide context to better interpret coronary computed tomographic angiographic measures and could be integrated into clinical decision making. (J Am Coll Cardiol Img 2024;17:165-175) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AI = artificial intelligence

AI-QCPA = Artificial Intelligence-Enabled Quantitative Coronary Plaque Analysis

CAD = coronary artery disease

CTA = computed tomographic angiography

CT = computed tomographic

FFR_{CT} = fractional flow reserve derived from computed tomographic coronary angiography

LAD = left anterior descending coronary artery

LCX = left circumflex coronary artery

PA = plaque analysis

Coronary computed tomographic angiography (CTA) is the established first-line imaging modality for the diagnostic work-up of patients with suspected coronary artery disease (CAD).[1] In addition, coronary CTA has now emerged as a tool for cardiovascular risk stratification on the basis of its ability to characterize and quantify the extent of atherosclerotic plaque. Plaque analysis (PA) software packages facilitate the quantitative assessment of coronary plaque volume and the identification of plaque subtypes on the basis of their attenuation density.[2] These PA tools have demonstrated that the type and amount of plaque enable refinement of cardiovascular risk stratification.[3,4] In a recent analysis, adverse coronary plaque characteristics and overall calcified plaque burden were associated with a higher risk for cardiac death or nonfatal myocardial infarction.[5,6] In addition, coronary heart disease rates differ between men and women, with additional variation in prevalence according to age.[7] This is likely related to sex differences in plaque burden, composition, and progression. However, there is a paucity of nomographic quantitative plaque data by age and sex distribution.

With growing adoption of coronary CTA, there is increasing interest in and evidence for the prognostic importance of total atherosclerotic plaque volume and plaque subtypes. Unfortunately, manual tools for quantitative assessment of atherosclerotic plaque are cumbersome and exhibit varying degrees of reproducibility.[8] In addition, it is unclear how to integrate quantitative plaque measures into clinical practice, partly because of a lack of nomographic data. We therefore sought to use an AI-QCPA (Artificial Intelligence-Enabled Quantitative Coronary Plaque Analysis) method to define age- and sex-specific nomograms of coronary atherosclerotic plaque volume.

METHODS

STUDY DESIGN. We conducted an observational, retrospective, consecutive, international, multicenter cohort study of patients who underwent clinically indicated coronary CTA between January 2021 and May 2022 across 29 health care systems in 2 countries (Canada and the United States). All sites provided local institutional approval to analyze and publish any metadata available from the AI-QCPA. Patients were included only if age and sex demographics were available and coronary computed tomographic angiographic (CT) images were of acceptable quality for quantitative plaque assessment. Patients <18 years of age were excluded from the final cohort. From an initial cohort of 15,447 patients, a total of 11,808 patients without any exclusion criteria were included in the final analysis (**Figure 1**). Image acquisition was performed using different vendors of CT scanners, including Siemens, GE Healthcare, Toshiba/Canon, and Philips (Supplemental Table 1).

AI-QCPA. All coronary CTA studies were analyzed for total plaque volume and for calcified plaque, noncalcified plaque, and low CT attenuation plaque volumes. AI-QCPA and measurements were performed using a software service (HeartFlow). AI-QCPA relies on AI algorithms and a human quality review process for the generation of a patient-specific 3-dimensional model of the arterial lumen. For each case, the aorta and the vessel centerlines of the coronary arteries were extracted from the best image quality phase using automated algorithms. The lumen and outer vessel wall were segmented with deep learning algorithms trained on thousands of coronary CT angiographic images and ground-truth models. Each of these datasets was quality checked, and luminal boundaries were modified if necessary by certified CT analysts using a predefined process and a custom workstation for inspection of AI algorithm results and coronary CT angiographic image data. Between the lumen and the outer wall, plaque presence was detected using a deep learning algorithm, plaque volume was quantified, and plaque was characterized using automatic thresholding on the basis of HU (low CT attenuation plaque, <30 HU; calcified plaque derived with adaptive thresholding on the basis of lumen contrast; and noncalcified plaque, >30 HU and less than the calcified plaque threshold) (**Figure 2**). See the Supplemental Methods for a detailed description of the methodology, training and validation of the AI-QCPA tool on the basis of the Proposed Requirements for Cardiovascular Imaging-Related Machine Learning Evaluation checklist.[9]

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD. Categorical variables are presented as number (percentage). Nomograms were developed from the entire CT cohort by plotting percentiles (10th, 20th, 30th, 40th, 50th, 60th, 70th, 80th, and 90th) of the various plaque volumes at the different age groups (<45, 45-55, 56-65, 66-75, and >75 years) for male and female patients, as well as for the entire population. Polynomial curves (second order) were subsequently fitted to each percentile (10th, 20th, 30th, 40th, 50th, 60th, 70th, 80th, and 90th) using the least squares method. Comparisons

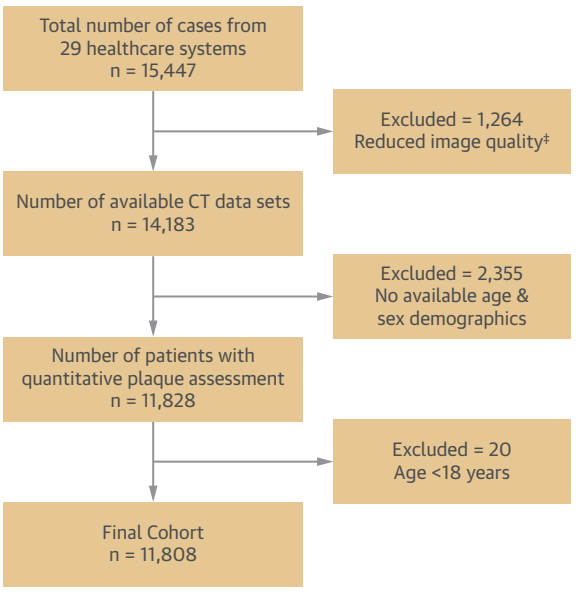
between 2 groups were performed using analysis of variance. Values of $P < 0.05$ were considered to indicate statistical significance. All statistical analysis were performed using SAS software version 9.4 (SAS Institute).

RESULTS

A total of 11,808 patients were included in the analysis; their mean age was 62.7 ± 12.2 years, and 6,385 (54.1%) were men. The distribution between male and female patients in each age group is represented in Supplemental Figure 1. The distributions of age in the total population and in male and female patients are presented in Supplemental Figure 2. The prevalence of physiologically significant or obstructive CAD in the entire total population on the basis of fractional flow reserve derived from CT coronary angiography (FFR_{CT}) in relation to sex and to age group and sex is illustrated in **Table 1** and Supplemental Table 2, respectively. The total plaque distributions in the entire population and in male and female patients are illustrated in Supplemental Figure 3. Age- and sex-related differences in plaque composition in a per-vessel analysis are reported in Supplemental Table 3. The distribution of total plaque volume was reported in every decile by age and total population (**Central Illustration**) and by age and sex (**Figure 3**).

The mean and median total plaque volume were 414 ± 515 mm^3 and 223 mm^3 (IQR: 29-614 mm^3), respectively. As expected, total median plaque volume was higher overall in male patients (360 mm^3; IQR: 78-805 mm^3) compared with female patients (108 mm^3; IQR: 10-388 mm^3) ($P < 0.0001$) (**Table 2**). This trend was also observed for all plaque components, with female patients on average having less calcified plaque, noncalcified plaque, and low CT attenuation plaque volumes than male patients (**Table 2**). The distributions of calcified plaque, noncalcified plaque, and low CT attenuation plaque were also reported in deciles by age group and total population (Supplemental Figure 4) and by age group and sex (Supplemental Figure 5). Total plaque volume and all component plaque volumes increased with age in both male and female subjects. The volume of noncalcified plaque as a percentage of total plaque volume decreased with increasing patient age, while the amount of calcified plaque as a percentage of total plaque volume increased with increasing patient age (**Central Illustration**, **Figure 4**). The cumulative distribution of the nomographic CT quantitative plaque volume data by sex across 5 age groups is illustrated in Supplemental Figure 6. The distributions of total plaque burden and of all plaque burden components are summarized in Supplemental Table 4 and illustrated in Supplemental Figures 7 to 9.

FIGURE 1 Flowchart Illustrating Patient Selection



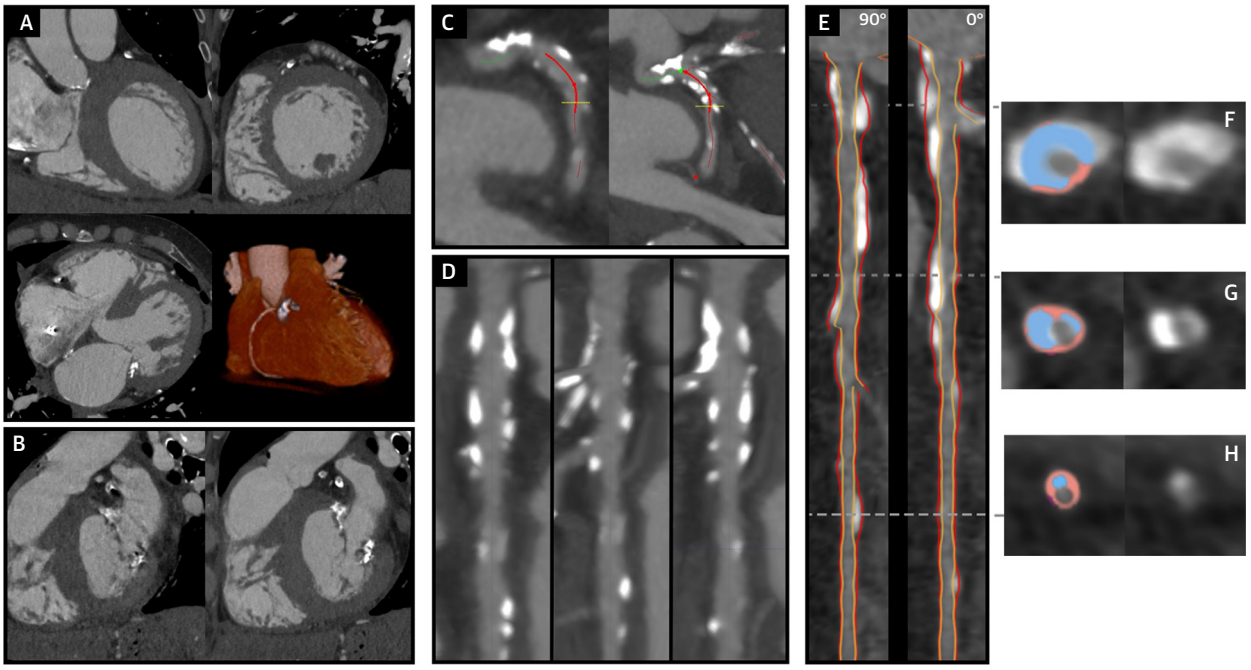
‡Reduced image quality (cases with motion artifacts and/or increased image noise).
CT = computed tomographic.

The prevalence of calcified plaque and noncalcified plaque in the entire population is illustrated in **Figure 5**. A considerable proportion of patients (12.5%) had only noncalcified plaque without having any coronary calcification. The proportions of patients with calcified plaque, noncalcified plaque, and noncalcified plaque but no calcified plaque according to age and sex are illustrated in **Figure 6**. Younger patients presented with noncalcified plaque more often than not. In addition, the proportion of patients with noncalcified plaque and no calcified plaque was higher in the younger age groups, irrespectively of sex.

DISCUSSION

Atherosclerotic plaque burden from CT imaging has been shown to be a powerful predictor of CAD risk and incident myocardial infarction. However, to date, quantification of atherosclerosis has been limited in practice, as the plaque quantification tools available have been limited because of the historical manual nature of these tools and the lack of clinical meaning of quantitative plaque volume. To that end, we have provided age- and sex-specific nomograms for total atherosclerotic plaque volume measurements and for

FIGURE 2 A Stepwise Explanation of AI-QCPA on Coronary CTA



(A) Raw coronary computed tomographic angiographic (CTA) datasets. (B) Select coronary CTA images with the best image quality. (C) Automated extraction centerline algorithm of the coronary arteries (green line). The red line indicates that the centerline is double-checked by the CT analyst. (D) Straightened multiplanar reconstruction (MPR) images are reconstructed from the initial centerlines. Lumen contours are automatically detected in 3 longitudinal cuts. (E) Automated segmentation of the lumen (orange line) and of the outer vessel (red line) in 2 straightened MPR images with a 90° difference. (F to H) Cross-sectional coronary CTA images with and without color overlay demonstrating the automated quantitative plaque assessment on the basis of HU attenuation (cyan, calcified plaque; pink, noncalcified plaque; purple, low CT attenuation plaque). AI-QCPA = Artificial Intelligence–Enabled Quantitative Coronary Plaque Analysis.

all plaque subtypes using an AI-QCPA of coronary CTA datasets from a large multicenter cohort. These findings could provide a clinically pragmatic approach for quantifying plaque volumes on an individual patient level and relative to the disease burden observed in patients of the same age and sex and further aid in risk-stratifying patients.

TABLE 1 Prevalence of Obstructive Coronary Artery Disease in the Entire Population Based on FFR_{CT} in Relation to Sex

	Combined (N = 11,808)	Female (n = 5,423)	Male (n = 6,385)	*P* Value
FFR_{CT} >0.8	4,926 (41.8)	2,830 (52.2)	2,096 (32.9)	<0.0001
FFR_{CT} ≤0.8 (any vessel)	6,869 (58.2)	2,588 (47.8)	4,281 (67.1)	<0.0001
Single vessel	4,331 (63.1)	1,771 (68.4)	2,560 (59.8)	<0.0001
2-vessel	1,903 (27.7)	643 (24.9)	1,260 (29.4)	<0.0001
3-vessel	635 (9.2)	174 (6.7)	461 (10.8)	<0.0001

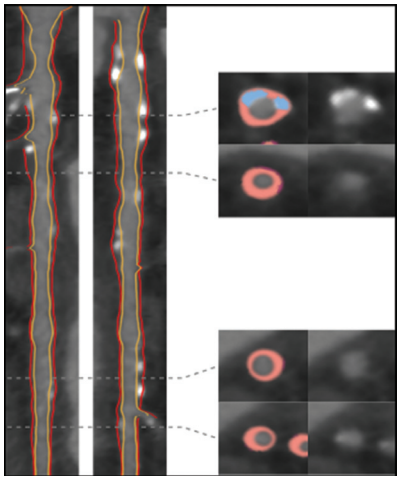
Values are n (%).
FFR_{CT} = fractional flow reserve derived from computed tomographic coronary angiography.

Our findings confirm prior studies showing that total plaque volume increased with age for both sexes and that male patients develop plaque earlier and have more plaque than female patients when adjusted for age.[10-12] Furthermore, men were found to have significantly higher coronary plaque subtype volumes, with predominance of noncalcified plaque, compared with women of the same age. Average volumes of all coronary plaque subtypes increased with age. In addition, noncalcified plaques were still present in 12.5% of all cases, further highlighting that coronary CTA could be used as an alternative risk stratification tool in patients with CAD. Interestingly, younger patients predominantly presented with noncalcified plaque, with the amount of noncalcified plaque as a percentage of total plaque volume decreasing with increasing age. In contrast, the amount of calcified plaque as a percentage of total plaque volume increased with increasing age. These findings show the relationship between the different plaque subtypes and could reflect the natural time course of coronary atherosclerotic plaque

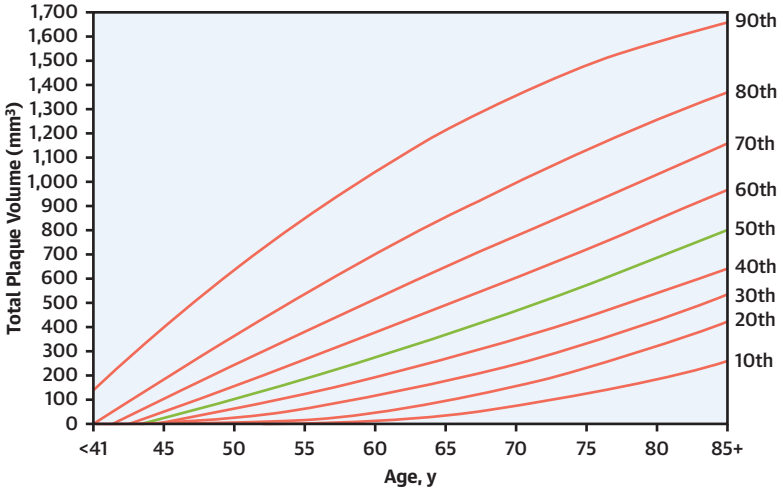
CENTRAL ILLUSTRATION **Age- and Sex-Specific Nomographic Coronary CTA AI-QCPA Data From a Large International Cohort**

January 2021 - May 2022
N = 11,808
Mean Age: 62.7 + 12.2 Years; n = 5,423 (45.9%) and n = 6,385 (54.1%)

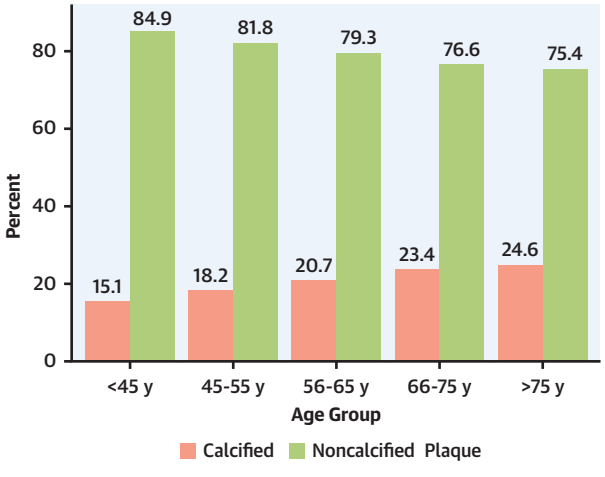
A AI-QCPA on Coronary CTA



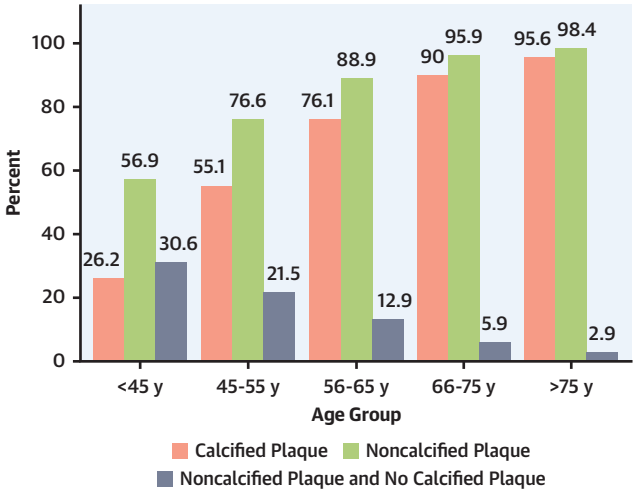
B Total Plaque Volume (mm³) ↗ With ↗ Age



C % Calcified Plaque Volume ↗ % Noncalcified Plaque Volume ↙ With ↗ Age



D Prevalence of Calcified Plaque and Noncalcified Plaque by Age



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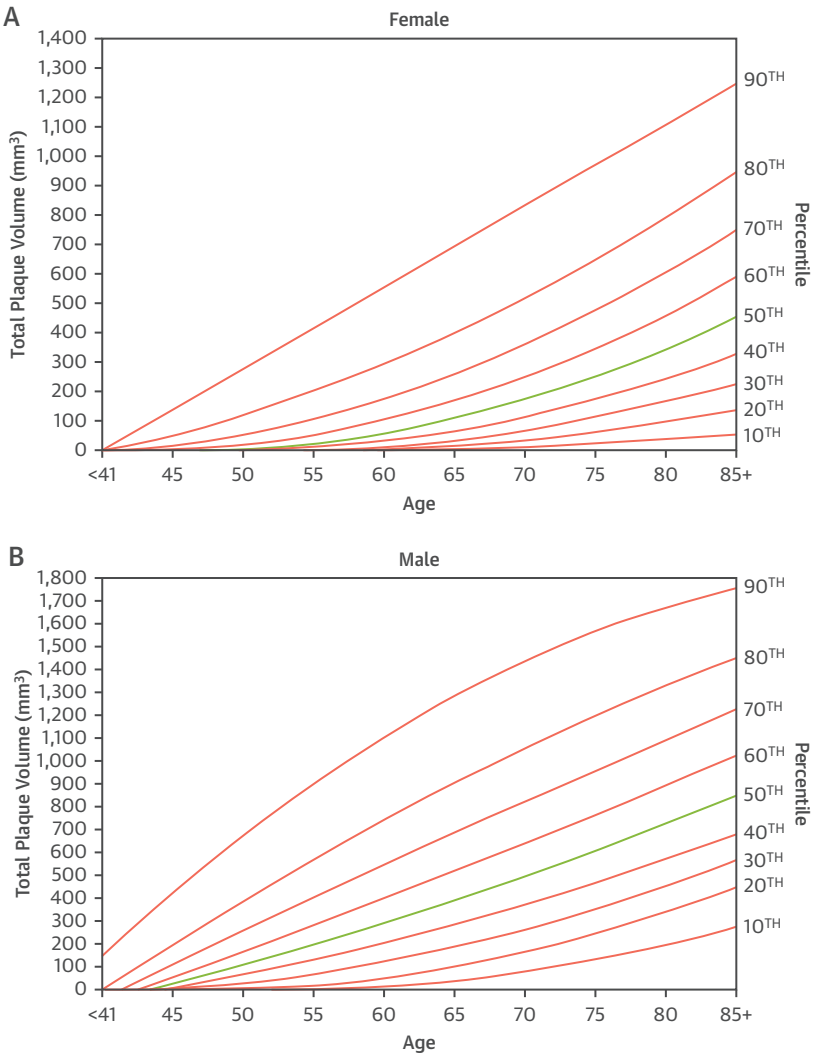
(A) Artificial Intelligence-Enabled Quantitative Coronary Plaque Analysis (AI-QCPA) on coronary computed tomographic angiography (CTA). (B) Distribution of total plaque volume reported in deciles by age and total population. (C) Percentage calcified plaque and noncalcified plaque volumes by age in the entire population. (D) Prevalence of calcified plaque and noncalcified plaque and of noncalcified plaque without coronary calcifications by age in the entire population.

FIGURE 3 Distribution of Total Plaque Volume Reported in Deciles by Age and Sex



(A) Female patients. (B) Male patients.

progression. Although it has been shown that coronary calcification is an independent risk factor for future adverse events,[13] there is growing awareness of the limitations of coronary calcium to track plaque progression.[14,15] In a recent analysis with serial coronary CTA, the investigators showed that increasing calcification, when considered as a percentage of total plaque volume, is a marker of plaque stability, with associated reduced risk for adverse effects at both the lesion and patient levels.[16] Further assessment of total plaque volume, plaque subtype volumes, their relationship, and risk is required to better understand how these factors relate.

Overall, total plaque volume was highest in the left anterior descending coronary artery (LAD) and lowest in the left circumflex coronary artery (LCX). In addition, for all plaque subtypes, the LAD contained the highest plaque volume, followed by the right coronary artery, the LCX and the left main coronary artery. These results align with findings from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) registry, wherein the prevalence of atherosclerotic plaque across the different coronary arteries was lowest in the LCX, followed by the right coronary artery and LAD.[17] Furthermore, a similar pattern of

plaque prevalence across the coronary vessels was also observed in the ICONIC (Incident Coronary Syndromes Identified by Computed Tomography) registry,[18] further highlighting the fact that these volumetric plaque measurements support a diverse milieu for plaque progression.

Although left main total plaque volume measurements were lowest across the different coronary arteries, its prevalence was not negligible at early ages. In a subanalysis of the ICONIC registry, the prevalence of nonobstructive left main disease was associated with a higher risk phenotype of atherosclerosis. Patients with left main disease were found to have higher total plaque volume, higher volumes of all plaque subtypes, higher adjusted calcified plaque progression, and more plaques with high-risk features.[19] More important, nonobstructive left main disease was found to be strongly associated with adverse events among female patients,[20] further emphasizing the sex-specific prognostic importance of nonobstructive left main CAD.

Despite a prevailing clinical perception that the incidence of coronary atherosclerosis increases progressively with age and that the prevalence of CAD is higher in male than in female patients, the extent of total atherosclerotic plaque volume and of all plaque subtypes by year of life and by sex is poorly documented. In a subanalysis of the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes) registry, nomograms based on age-sex percentiles of segment involvement score were provided, showing that overall atherosclerotic plaque burden provides additional prognostic value, independently of traditional risk assessment;[21] however, these nomograms were limited to description of the segmental involvement score. In a more recent analysis, a staging of plaque burden on the basis of atherosclerotic plaque volume measurements and its relationship with the extent and severity of coronary stenosis severity as well as the presence of myocardial ischemia was described.[22] The investigators suggested a 4-stage classification approach on the basis of thresholds for total plaque volume and percentage atheroma volume in which patients with no CAD, nonobstructive CAD, single-vessel disease, and multivessel disease were distributed. Although the study was stratified by age and sex, the interaction of both factors were not incorporated into the plaque stages, thus limiting their prognostic value. On that premise, age- and sex-specific AI-QCPA nomograms could provide context to better interpret coronary CTA measures and guide clinical decision making.

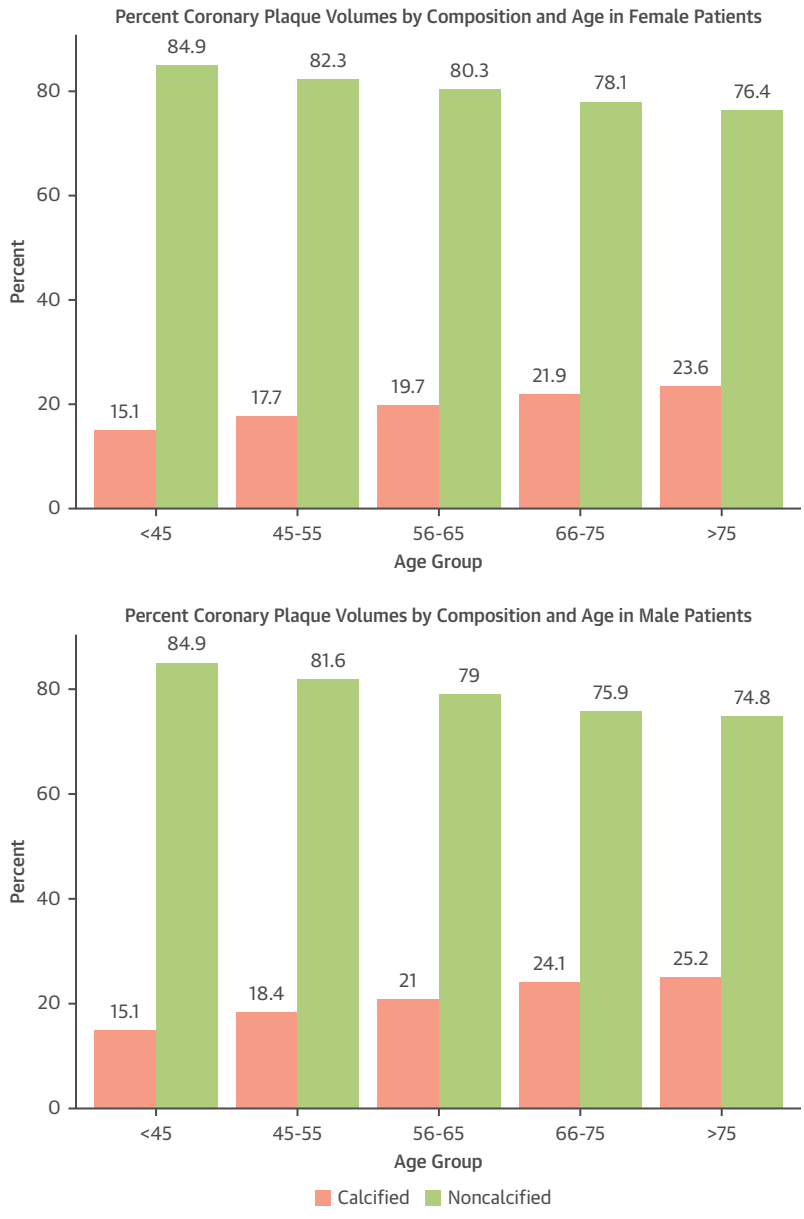
TABLE 2 Patient and Plaque Volume Characteristics

	Combined (N = 11,808)	Female (n = 5,423) (45.9%)	Male (n = 6,385) (54.1%)	*P* Value
Age, y	62.7 ± 12.2 (18-101)	63.4 ± 12.5 (18-101)	62.0 ± 11.9 (18-95)	<0.0001
TPV, mm^3	413.5 ± 515.0 (0-4,913) 223 (29-614)	271.9 ± 381.6 (0-3,041) 108 (10-388)	533.8 ± 579.1 (0-4,913) 360 (78-805)	<0.0001
CPV, mm^3	92.6 ± 148.6 (0-2,229) 31 (1-122)	58.8 ± 102.8 (0-1,202) 12 (0-73)	121.3 ± 173.4 (0-2,229) 55 (5-168)	<0.0001
NCPV, mm^3	320.9 ± 380.1 (0-3,028) 184 (27-486)	213.0 ± 288.4 (0-2,497) 93 (10-309)	412.5 ± 422.3 (0-3,028) 296 (69-623)	<0.0001
LAPV, mm^3	9.0 ± 11.9 (0-144) 5 (0-13)	5.7 ± 8.5 (0-85) 2 (0-8)	11.8 ± 13.5 (0-144) 8 (2-17)	<0.0001

Values are mean ± SD, range (minimum-maximum), or median (IQR).
CPV = calcified plaque volume; LAPV = low computed tomographic attenuation plaque volume; NCPV = noncalcified plaque volume; TPV = total plaque volume.

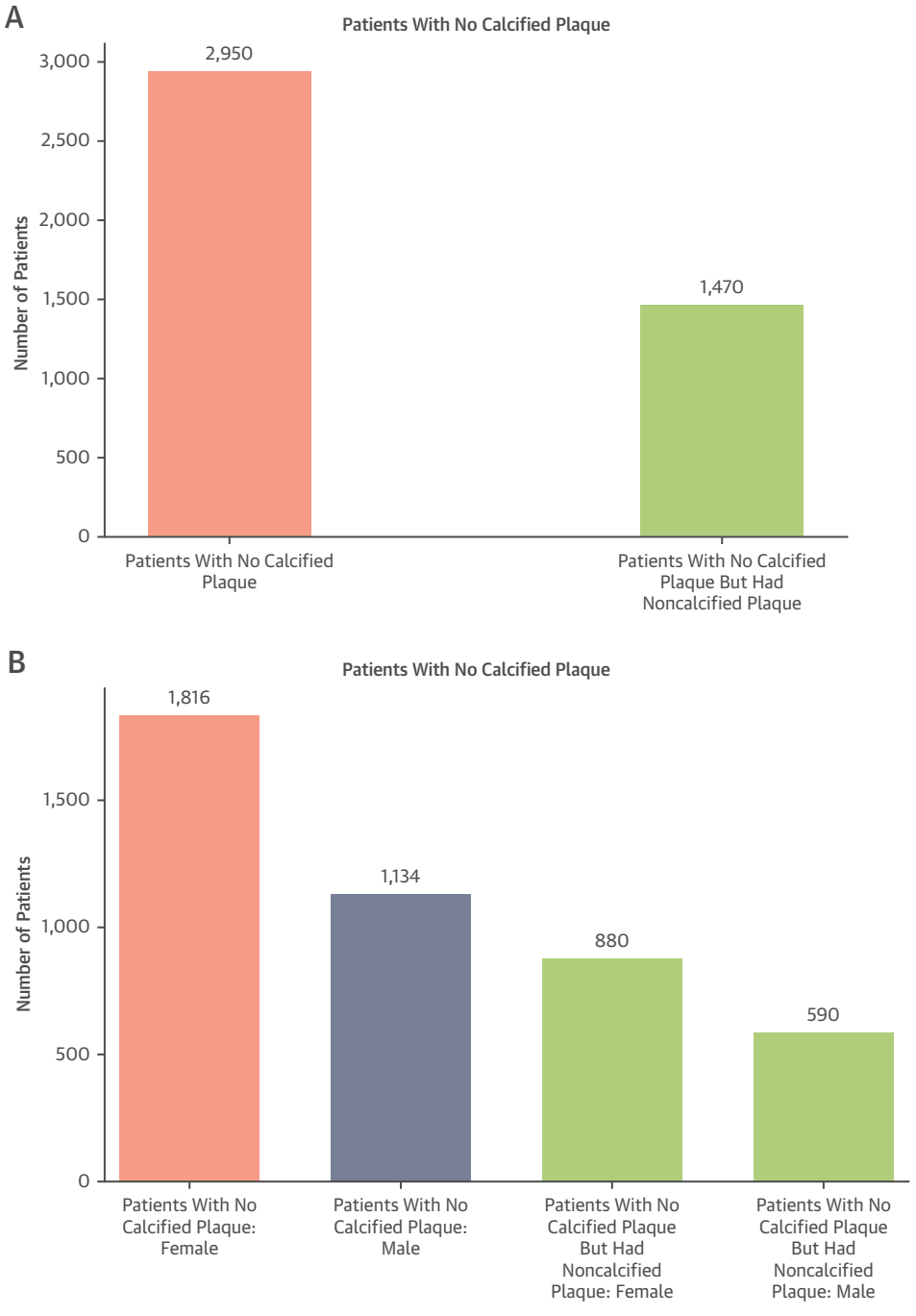
STUDY LIMITATIONS. The study had a number of important limitations, including a lack of clinical outcomes on the cohort studied. Importantly, though, this was a real-world, consecutive patient clinical cohort, which was therefore not plagued with the inherent inclusion biases of registries. We also lacked patient characteristics such as cardiovascular risk factors, symptom status, previously known diagnosed CAD, medications, and ethnicity. However, we provide information regarding the prevalence of obstructive CAD in the entire total population on the basis of noninvasive physiology derived from FFR_{CT}. Of note, the lowest FFR_{CT} value, whether distal to the stenosis in the presence of a focal lesion or in the terminal vessel in the presence of serial stenoses was used for this analysis. As such, the values reported are likely a blend of lesion-specific physiology, in the setting of a focal lesion, and nadir values in the setting of diffuse disease. Given this, the reported reference FFR_{CT} values may be applicable for populations of symptomatic patients with high prevalence of obstructive CAD and that these values may be less representative of populations with lower prevalence of obstructive CAD, often seen in typical clinical coronary CTA populations. Further investigation validating the use of the nomograms in population-based cohort studies is needed to confirm the potential role of AI-QCPA as a risk tool for guiding clinical decision making in addition to traditional risk factor assessment. In addition, we did not compare plaque volumes with a reference standard, such as intravascular ultrasound, although this has been previously reported by others.[23,24] Futures

FIGURE 4 Percentage Coronary Plaque Volumes by Composition and Age in Female and Male Patients



studies with external validation are required for this to become accepted and part of clinical practice. The agreement between the AI-QCPA tool and manual quantification for low-attenuating plaque was modest. This is in line with prior studies showing that low CT attenuation plaque is an unstable measure, particularly when being assessed on a per-patient basis, because of the impact of image noise on total low CT attenuation plaque and the relatively modest amount of low CT attenuation plaque. Whether low CT attenuation plaque remains a valued component of overall PA or perhaps a focus of lesion level characterization remains to be determined. The exclusion ratio due to inadequate image quality for the nomographic cohort was 8.2%, similar to previous studies.[25] Last, our cohort was not a community population screening cohort. However, an important element of our study is its pragmatic nature, as the patients included all underwent clinically indicated coronary CTA, so our nomograms reflect the prevalence of CAD in day-to-day clinical practice across multiple centers.

FIGURE 5 Prevalence of Calcified Plaque and Noncalcified Plaque in the Entire Population

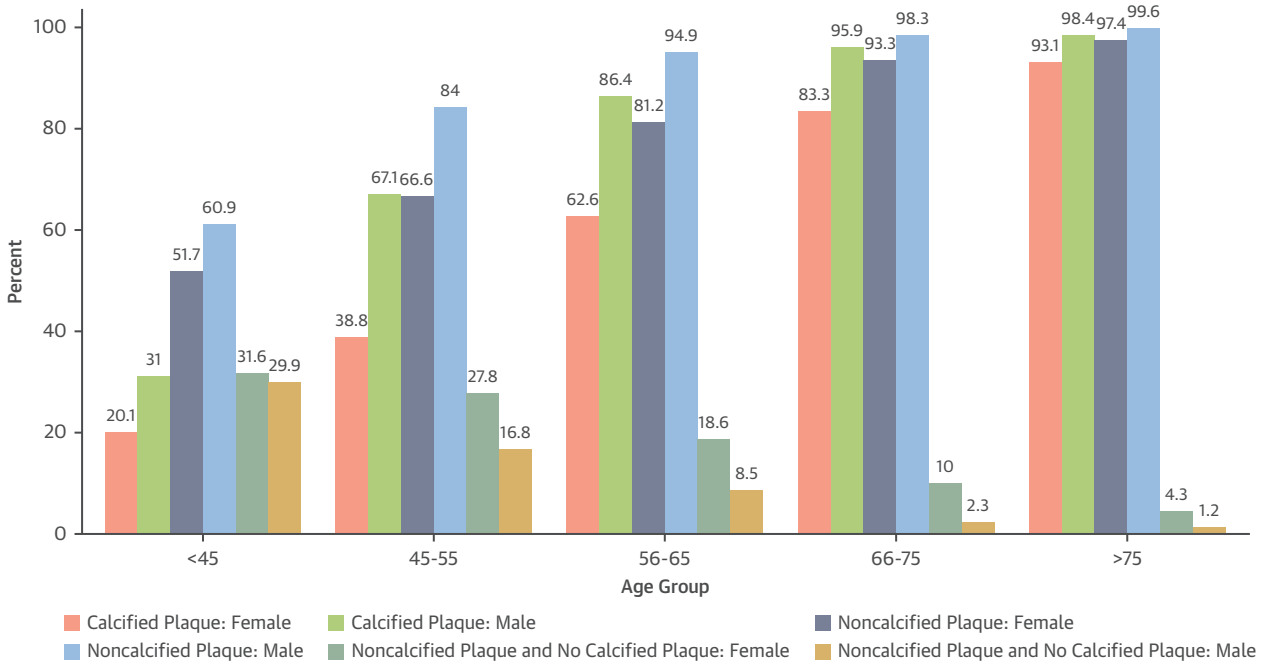


(A) Total population. (B) Female and male patients.

CONCLUSIONS

We present age- and sex-stratified percentile nomograms for atherosclerotic plaque volumes on the basis of coronary CTA from a new AI-QCPA tool. These findings could provide context for quantitative plaque volumes to allow clinical integration and to help inform clinical decision making. Our study

FIGURE 6 Prevalence of Calcified Plaque and Noncalcified Plaque According to Age and Sex



provides a nomographic framework, but future studies are needed to evaluate the relationship with downstream clinical outcomes and whether quantitative plaque informs clinical decision making in a fashion that improves outcomes beyond visual assessment.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Age- and sex-related differences in the expression of CAD should be considered when CT quantitative plaque assessment is performed. The prevalence of noncalcified plaque among patients with detectable but no calcified plaque is high, especially in younger patients.

TRANSLATIONAL OUTLOOK: A better understanding of CT quantitative plaque volumes according to age and sex may help inform clinical decision making. This could be of utmost importance, especially in specific subgroups of patients (younger patients), for the possible future advent of targeted atherosclerosis treatment.

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APPENDIX For an expanded Methods section as well as supplemental figures, tables, and references, please see the online version of this paper.