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Adverse Cardiovascular Events Among Younger and Older Patients Referred for Coronary CTA: The Mass General Brigham CCTA Registry

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Abstract

Background: Recent guidelines suggest that coronary CTA (CCTA) may be the preferred testing modality in patients <65 years who are suspected of having coronary artery disease (CAD). Due to a higher prevalence of CAD, the role of CCTA in older cohorts is less well established.

Objectives: We aimed to characterize the yield and prognostic utility of CCTA by age in a large registry with long term follow-up.

Methods: Retrospective cohort of patients clinically referred to CCTA at two medical centers from 2006–2021, excluding patients with prior CAD, severe renal disease, and malignancy. Adjusted Cox regression was used to assess the association of CAD severity (absent, nonobstructive, obstructive) and extent (number of vessels with plaque) with adverse CV events (MACE: CV death, nonfatal myocardial infarction, or ischemic stroke) across different age groups.

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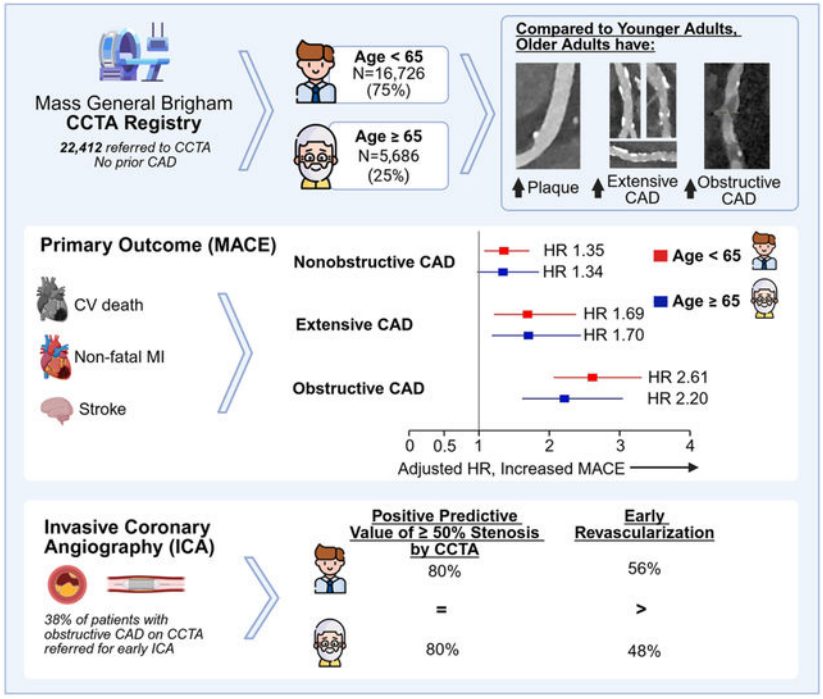
Results: Among 22,412 patients followed over a median of 6.2 (IQR 3.9–9.6) years, 16,726 were < 65 and 5,686 were ≥ 65. Older patients had a higher prevalence of obstructive CAD (38% vs 15%) and extensive plaque (52% vs 20% with 3–4 vessel involvement) compared to their younger counterparts. Nonobstructive plaque was common in both groups (<65: 37%; ≥65: 48%). Obstructive CAD was associated with MACE in both younger (HR 2.45, p<0.001) and older individuals (HR 1.97, p<0.001). Nonobstructive plaque was associated with MACE in younger individuals (HR 1.39, p=0.005), while only extensive nonobstructive CAD was associated with MACE in older individuals (HR 1.56, p=0.02). Among those with obstructive CAD on CCTA who underwent early invasive coronary angiography, revascularization was less common among older adults (48% vs 56%, p=0.002).

Conclusions: In a large CCTA registry, patients over the age of 65 were more likely to have extensive plaque and stenosis. While the prognostic value of CCTA may be lower among older adults with nonobstructive plaque (a group which has a similar event rate as those with no CAD), the presence of extensive nonobstructive plaque or obstructive stenosis was independently associated with a significantly higher rate of MACE. Newer techniques to better risk stratify patients with nonobstructive plaque may improve the value of CCTA, especially in older adults.

Central Illustration:



Prognostic utility, yield and positive predictive value of CAD findings on CCTA in older versus younger adults

Hazard ratios are in comparison to no CAD group and adjusted for sex, hypertension, dyslipidemia, diabetes, morbid obesity, chronic kidney disease, current smoking, prior stroke or TIA, atrial fibrillation, baseline statin use, setting of test. CCTA: coronary CT angiography; CAD = coronary artery disease; ICA = invasive coronary angiography

Condensed Abstract:

Coronary CTA (CCTA) is recommended for suspected CAD in patients <65, but its role in older adults is less established. This retrospective study of 22,412 patients compared CCTA findings and outcomes by age. Older adults (≥65) had more obstructive CAD and extensive plaque than younger patients. Obstructive CAD predicted major adverse cardiovascular events (MACE) in both groups, while nonobstructive plaque predicted MACE mainly in younger patients. In older adults, only extensive nonobstructive plaque was associated with MACE. CCTA remains a valuable prognostic tool for older adults, but further research is needed on advanced risk stratification and comparisons with functional testing.

Keywords

coronary computed tomography angiography; coronary artery disease; cardiovascular outcomes; age

Introduction

The prevalence of coronary artery disease (CAD) increases with age[1], including coronary artery plaque detected on coronary computed tomography angiography (CCTA)[2]. CCTA has high diagnostic accuracy and negative predictive value for obstructive CAD[3–5], and can provide comprehensive information about nonobstructive plaque including the presence of high-risk features[2,6,7]. Obstructive and nonobstructive CAD found on CCTA is associated with adverse cardiovascular outcomes[6,8,9]. However, most patients referred to CCTA and included in studies of the diagnostic and prognostic yield of CCTA are younger than 65 years[10,11]. Due to a higher pretest probability for CAD, higher rates of positive noninvasive testing[10,11], and higher calcified plaque burden potentially reducing diagnostic accuracy[12], the role of CCTA in older cohorts is less established.

Prior seminal outcomes studies have yielded mixed results regarding the prognostic utility of CCTA in older compared with younger patients. In the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry, both obstructive and nonobstructive coronary plaque were strongly associated with longitudinal adverse cardiovascular events among 15,187 patients followed for mean 2.4 years, including in those 65 years and older,[11] which was confirmed in long-term follow-up among those 70 years and older[13]. Conversely, among 4,500 patients followed for median of 25 months in the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) registry, obstructive findings on CCTA were not associated with CV death or MI among individuals aged 65–74 years (HR 0.67 [0.15–2.94]) and 75 years and older (HR 1.07 [0.22–5.34]), unlike in those less than 65 years (HR 3.04 [1.46–6.34])[10].

Reflecting the uncertainty of the diagnostic and prognostic utility of CCTA and the higher pretest probability of obstructive CAD in older adults, the 2021 Chest Pain Guideline indicated that stress testing may be preferable over CCTA in patients 65 years and older. However, there is only limited evidence for this recommendation[14], and several statements have suggested that knowledge about prior CAD and expected image quality are more

important in test selection than patient age[15]. As the use of coronary CTA has expanded[16], this test is being increasingly performed across the age spectrum. Accordingly, we aimed to characterize the yield and prognostic value of CCTA by age in a large registry of patients clinically referred for CCTA with a longer duration of follow-up compared with prior studies.

Methods

Study Population

The Mass General Brigham (MGB) Coronary Computed Tomography Angiography (CCTA) registry is a retrospective cohort constituting 28,189 patients who were referred primarily for symptoms suggestive of CAD to two major medical centers from 2006 to 2021 (Brigham and Women's Hospital and Mass General Hospital, Boston, MA). The current study included all adults ≥ 18 years of age who underwent a diagnostic CCTA without a prior history of known coronary artery disease including myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG), without advanced kidney disease including stage 5 CKD/end-stage renal disease or prior kidney transplant, and without life-limiting malignancy defined by International Classification Codes (ICD) codes. For patients with multiple CCTA studies, only the first was included. Full details of eligibility criteria are available in the supplementary materials (Supplementary Table 1A and Supplementary Figure 1). This study was approved by the MGB Institutional Review Board.

CCTA Acquisition, Interpretation, and Report Extraction

CCTA was acquired using a variety of 64-multidetector row or greater scanners while following institutional policies aligned with the Society of Cardiovascular Computed Tomography (SCCT) guidelines[17]. Both retrospective helical and prospective axial gating were utilized. Studies were visually interpreted according to SCCT guidelines by COCATS level III cardiology or radiology physicians using a structured reporting system.

The presence of plaque and degree of luminal stenosis was extracted on a per-vessel basis from CCTA reports, and associated coronary artery calcium (CAC) scores when available, using a validated natural language processing (NLP) approach developed with the open-source Canary NLP platform[18]. The accuracy of this approach in characterizing per-vessel luminal stenosis and the presence of plaque is greater than 95%[19]. Stenosis was further categorized using the Coronary Artery Disease Reporting and Data System 2.0 (CAD-RADS)[7] and then categorized into (1) absent plaque, (2) nonobstructive CAD: 0–50% (CAD-RADS 1–2), and (3) obstructive CAD: ≥ 50% stenosis (CAD-RADS 3–5). When the CAC score was greater than zero, and degree of stenosis was not reported or reported as none, stenosis was classified as nonobstructive. As a surrogate for plaque amount which was not clinically reported over the entire study period, plaque extent (number of vessels involved) was categorized from 0 to 4 with a point each for plaque in the left main, left anterior descending artery including diagonals and ramus intermedius, left circumflex including obtuse marginals, and right coronary artery. Plaque extent was further subcategorized into no plaque (0-vessels), non-extensive plaque (1–2 vessels), and extensive

plaque (3–4 vessels) among all patients and in the subset of patients with nonobstructive plaque.

Clinical Data

Clinical data including demographics (age, sex, race/ethnicity), vital status from the Social Security Administration, diagnostic and procedural codes, laboratory data, imaging data, clinical notes, and medication data was obtained through the MGB Research Patient Data Registry (RPDR) and Enterprise Data Warehouse (EDW), centralized registries of data extracted from the electronic health record. Cause of death and vital status was determined from International Classification of Diseases (ICD) coded data from the Massachusetts Office of Vital Statistics and the CDC National Death Index, as well as review of the electronic health record. Medical diagnoses at the time of the CCTA were determined based on ICD-9, ICD-10, Current Procedural Terminology (CPT) codes, and laboratory values as described in the supplemental methods (Supplemental Table 1B). Smoking status in the year of the CCTA was determined using a validated NLP approach[20]. Medication prescriptions in the two years prior and the one year after CCTA were obtained from electronic prescription data in the MGB EDW.

Outcomes

The primary outcome was major adverse cardiovascular events (MACE) defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke. Secondary outcomes included all-cause mortality, early referral to invasive coronary angiogram within 90 days of CCTA, early revascularization within 90 days, and late revascularization after 90 days. Cardiovascular cause of death was classified based on ICD-coded underlying cause of death from death certificates. Outcomes were determined from the electronic health record based on previously validated methods (Supplemental Methods, Supplemental Table 1C). All outcomes were censored in April 2024, the latest date of ascertainment.

Statistical Analysis

Baseline characteristics by age group were reported as frequencies (percentages) for categorical variables and median (interquartile range) for numerical variables. Numerical baseline characteristics were analyzed using Mann-Whitney U tests and categorical baseline characteristics were analyzed with chi-square tests of association or Fisher exact tests. Patients were censored at either the date of querying vital statistics or the date of death.

Univariable and multivariable Cox proportional hazards regressions were analyzed separately for patients who were less than or greater than or equal to 65 years to assess the association of CAD severity and plaque extent (number of vessels involved 0–4) with MACE (cardiovascular death, acute myocardial infarction, or stroke). Interaction terms between age group and plaque group were assessed in the multivariable Cox proportional hazard regression model to determine if the age group modified the association of plaque severity and extent with MACE. Sensitivity analyses assessed the association of plaque severity and extent with MACE for patients who were elderly, defined as age 75 years or greater. Cox models were reported as hazard ratios and 95% confidence intervals. Log-rank tests were used to compare Kaplan-Meier Curves. Annual incident rate ratios

and their 95% confidence intervals were reported for the primary MACE outcome for age groups mentioned above and compared with Poisson regression. Multivariable Cox regression models were checked for multicollinearity using Spearman rank correlation and proportional hazard assumptions with Schoenfeld residuals. Analyses were adjusted for the following covariates: sex, hypertension, dyslipidemia, diabetes, chronic kidney disease, current smoking status, morbid obesity (body mass index ≥ 40), prior stroke or transient ischemia attack (TIA), atrial fibrillation, baseline statin use and setting of test (outpatient, emergency, or inpatient).

We calculated the positive predictive value (PPV) of detecting stenosis on CCTA as the ratio of patients who were found to have obstructive CAD on invasive coronary angiography (ICA) to the total number of patients referred with obstructive CAD on CCTA. Proportion revascularized was calculated as the ratio of the number of patients with obstructive CAD on CCTA who were revascularized (PCI or CABG) to the total number of patients referred to ICA with obstructive CAD. Proportions were compared between age groups using chi-square test.

Subgroup analyses were performed in predefined groups including male vs female sex, severe coronary artery calcification (Agatston calcium score > 300) versus moderate or less, and for increasing number of traditional cardiovascular risk factors from 0 to 4 (hypertension, diabetes, dyslipidemia, current smoking). Interaction terms between the subgroup categories and plaque severity were assessed in the multivariable Cox proportional hazard regression model to determine effect modification. Sensitivity analyses were performed to test the robustness of our results. These included: (1) defining the primary outcome as cardiovascular death or nonfatal myocardial infarction (without stroke); (2) defining the primary outcome as cardiovascular death, nonfatal myocardial infarction, or late revascularization; (3) and including early revascularization as an adjustment factor in the regression model.

All analyses were performed using SAS Version 9.4 (Cary, NC) and Stata MP Version 18 (StataCorp, College Station, TX). Two-tailed tests with an alpha value of 0.05 were considered statistically significant.

Results

Baseline Characteristics and Prevalence of Plaque on CCTA

Among 22,412 patients referred to CCTA from 2006 to 2021 without prior CAD, and followed for a median of 6.2 (IQR 3.9–9.6) years, the median age was 56 (IQR 47–65) and 45% were female. Nearly 75% of patients were under the age of 65 (16,726). Patients 65 years of age or older had a higher prevalence of cardiovascular risk factors including hypertension, diabetes, and CKD as well as a lower median BMI and were less likely to be active smokers (Table 1).

Older patients had a higher prevalence of having any plaque (85% vs 52%), obstructive CAD (38% vs 15%), and more extensive CAD (52% vs 20%) and a lower prevalence of absent plaque (15% vs 48%) compared with younger patients. In younger and older

patients with plaque, most had nonobstructive plaque (Younger: 6,113/8,703, 70% and Older: 2,708/4,845, 56%) rather than obstructive CAD (Table 2). Over the CCTA referral period, the prevalence of nonobstructive plaque increased and the prevalence of obstructive plaque decreased in both age groups (Figure 1). Older adults had a higher cumulative incidence of MACE (8.8% vs 3.0%) and other individual outcomes, and a shorter median follow-up duration (5.1 vs 6.5 years) (Supplemental Table 2). Finally, older adults had a higher prevalence of one or more nondiagnostic coronary segments (15% vs 11%); the prevalence significantly declined in both age groups over the study period (Supplemental Table 3).

Unadjusted and adjusted association of plaque on CCTA with MACE stratified by age group

Outcomes Among Adults <65: Among patients under the age of 65, both nonobstructive plaque (HR 1.73, 95% CI 1.38–2.16, p<0.001) and obstructive plaque (HR 4.33, 95% CI 3.49–5.37, p<0.001) was associated with MACE compared with those without plaque. After adjustment for demographics and CV risk factors, nonobstructive plaque (HR 1.35, 95% CI 1.07–1.71, p=0.01) and obstructive plaque (HR 2.61, 95% CI 2.06–3.31, p<0.001) continued to be associated with the occurrence of MACE (Table 3 and Figure 2). Among patients with nonobstructive plaque, an increasing number of vessels involved was associated with a stepwise increase in MACE, with the highest risk among those with extensive (3–4 vessel) involvement (HR 1.69, 95% CI 1.21–2.38, p=0.002 compared to 0-vessel involvement, Figure 3).

Outcomes Among Older (age≥65) Adults: Among patients 65 years of age and over, both nonobstructive plaque (HR 1.38, 95% CI 1.00–1.90, p=0.048) and obstructive plaque (HR 2.57, 95% CI 1.89–3.49, p<0.001) was associated with MACE compared to those without plaque. After adjustment for demographics and CV risk factors, obstructive plaque (HR 2.21, 95% CI 1.61–4.05, p<0.001) continued to be associated with the occurrence of MACE, however nonobstructive plaque was no longer significantly associated (HR 1.34, 95% CI 0.97–1.85. p=0.08). (Table 3 and Figure 2). Among patients with nonobstructive plaque, extensive plaque (3–4 vessel) involvement was associated with increased MACE (HR 1.70, 95% CI 1.18–2.45, p=0.005) while non-extensive plaque (1–2 vessel) involvement was not (p=0.68), compared to 0-vessel involvement (Figure 3).

In the subpopulation of elderly patients who are 75 and over, obstructive plaque but not nonobstructive plaque was associated with MACE, and the risk for MACE was moderate to high (>1% annually) regardless of plaque findings (Figure 4).

Comparing Younger vs. Older Population

In adjusted Cox regression examining the interaction of age group and plaque group, obstructive CAD was associated more strongly with MACE among patients under the age of 65 compared with those 65 and over (HR 2.61vs HR 2.21, p value for interaction 0.03). Nonobstructive plaque was associated with MACE at a similar strength (HR 1.35 vs HR 1.34 compared to absent plaque, p value for interaction 0.31). Finally, extensive

nonobstructive plaque (3–4 vessel) was associated with MACE at a similar strength when comparing those under the age of 65 with those 65 and over (HR 1.62 vs 1.89, p=0.29).

Positive predictive value for Obstructive CAD on Invasive Coronary Angiography (ICA)

A minority of patients underwent early ICA (within 90 days), 7% in the <65 group and 15% in the 65+ group, with the highest proportion in those with obstructive findings on CCTA (39% and 38% respectively) (Table 4). Of those who underwent ICA with suspected obstructive CAD (≥50% stenosis) on CCTA, the positive predictive value (PPV) for obstructive CAD on ICA (≥50% stenosis) was 794/998 (80%) for those <65 and 645/806 (80%) for those ≥65, and the proportion who underwent early revascularization was 555/998 (56%) and 390/806 (48%) respectively (p=0.002).

Subgroup analysis of the association of MACE by sex, number of cardiovascular risk factors, and CAC score

Nonobstructive and obstructive plaque findings on CCTA were generally associated with MACE regardless of sex, whether in the presence of severe coronary artery calcification (CAC > 300), and regardless of the number of traditional cardiovascular risk factors (hypertension, dyslipidemia, diabetes, current smoking in a range from 0 to 4 risk factors (Supplementary Table 4 A and B). However, in patients 65 years of age and over who were female, obstructive plaque was more strongly associated with MACE compared to males ≥65 (HR 3.03 vs 1.35, p value for interaction between sex and obstructive plaque p=0.02). Conversely in patients younger than 65 who were female, obstructive plaque was less strongly associated with MACE compared with males (HR 1.98 vs 3.04, p value for interaction between sex and obstructive plaque p=0.045).

Sensitivity Analysis

The findings were unchanged in sensitivity analysis while adjusting for early revascularization (within 90 days), and when defining the primary outcome as cardiovascular death or myocardial infarction (Supplemental Figure 2 and Supplemental Table 5) and when defining the primary outcome as cardiovascular death, myocardial infarction or late revascularization (Supplemental Figure 3 and Supplemental Table 6).

Discussion

Among both younger and older adults, we found that CCTA findings are strongly associated with adverse cardiovascular events with similar positive predictive value for detecting obstructive CAD (Central Illustration). Although patients 65 years of age or older had higher burden of both nonobstructive and obstructive plaque and increased cardiovascular risk regardless of CAD severity compared with younger adults, CCTA continued to stratify risk of future ASCVD events. However, the prognostic value of CCTA in older individuals was mostly attributable to the higher risk associated with obstructive CAD or extensive plaque, while in young individuals there was also prognostic value related to the presence of non-obstructive plaque – a finding which was associated with a higher risk of MACE. Notably, even in those 75 years of age or older, obstructive CCTA findings were associated with an increased risk.

Among older adults, nonobstructive plaque was highly prevalent, and increased over the study period. While older adults had a higher prevalence of plaque, only those with extensive plaque (i.e. involving at least 3 vessels) were at higher risk. Conversely, among younger adults, nonobstructive plaque was associated with risk regardless of the number of vessels involved. When evaluating the association of obstructive CAD with outcomes by age groups, we found that older adults with obstructive CAD had a less robust association with MACE compared with younger individuals, although this finding may reflect the higher baseline risk of older adults. The higher calcified plaque amount in older adults has been associated with reduced diagnostic accuracy for obstructive CAD[12], which could attenuate the association of obstructive CAD with MACE. A higher proportion of older patients had one or more nondiagnostic coronary segments (Table 2, Supplementary Table 3), which may reduce overall diagnostic accuracy and therefore attenuate associations between plaque severity and MACE; however, we found similar PPV among younger and older adults who were referred for invasive coronary angiography.

We also found a sex-based difference when examining the association of CCTA with hard cardiovascular events, whereby in older males obstructive plaque was less predictive of cardiovascular events compared with older females (p for interaction 0.003). Conversely, obstructive plaque was highly predictive of MACE among younger males. The higher prevalence of plaque among older males and the high baseline cardiovascular risk even in those with absent plaque may explain these findings.

Our findings reinforce the need for additional methods to risk stratify individuals with non-obstructive and obstructive CAD. Among individuals with non-obstructive plaque, investigational techniques include quantitative coronary plaque analysis or the fat attenuation index (FAI)[21], and additional studies should evaluate the incremental prognostic value of these tests among older and younger individuals with non-obstructive CAD. Among symptomatic individuals with obstructive CAD who are being considered for coronary revascularization, functional testing including FFR-CT or stress testing may help refine risk and inform the potential benefit of coronary revascularization[22].

It has been well established that nonobstructive and obstructive plaque on CCTA are associated with increased cardiovascular risk. However, it is less well established whether this association remains in those who are 65 and over. The CONFIRM registry is the largest previous registry of patients which has investigated association of plaque in older adults and has consistently found that both obstructive and nonobstructive plaque are associated with outcomes[11] including in longer term follow-up in adults 70 and over[13]. The MGB CCTA registry is a more contemporary and larger registry, with longer follow-up until 2024. In addition, while the CONFIRM registry used a composite outcome which included all-cause mortality and coronary revascularization, our study used a composite of hard cardiovascular events. The findings of the current study from the MGB CCTA registry further support the prognostic value of CCTA in older individuals and also provides evidence that positive predictive value for detecting obstructive CAD on subsequent ICA is high (80%) even among older adults. However, despite the fact that the majority of patients who were referred to invasive angiography after being found to have obstructive CAD on CCTA, had obstructive CAD on invasive angiography, there was a smaller proportion of older adults

who were ultimately revascularized (48% vs 56%). These findings may reflect the more conservative use of coronary revascularization in older adults, a group where there may be a higher risk of complication of interventions and of long term dual anti-platelet agents. However, this finding suggests that some older individuals may not have required invasive angiography. Indeed, while our study supports the prognostic value of CCTA in older adults, the optimal non-invasive imaging test in this population remains unknown. Prior outcomes studies comparing CCTA with functional testing have been predominantly focused on younger populations, and did not include contemporary techniques (e.g. photon counting CT, or PET myocardial perfusion imaging using quantitative assessment of myocardial blood flow)[23–25]. Therefore, there is a need for contemporary studies comparing CCTA vs. stress testing among older high-risk individuals. Such studies should focus not just on cardiovascular outcomes, but also diagnostic accuracy.

Our results, and those of CONFIRM, contrast with the findings in the prospective trial PROMISE, which found that obstructive plaque was not associated with increased cardiovascular risk in adults older than 65, compared with those with nonobstructive or absent plaque[10]. In the PROMISE study, few patients 75 years and older were enrolled (N=526) and the median follow-up time was only 25 months, which may have reduced statistical power. Additionally, those with obstructive plaque were compared with the combined group of those with absent or nonobstructive plaque which does not account for the increased risk of nonobstructive findings on CCTA.

Our study has several limitations. The study was retrospective and subject to referral bias – older patients with a higher pre-test likelihood for obstructive CAD or nondiagnostic CCTA may have been referred to alternative imaging modalities. Furthermore, non-fatal cardiovascular outcomes occurring outside our healthcare system were not available, potentially leading to an underestimation of MACE rates. Nonetheless, in sensitivity analysis using the last medical encounter date rather than last ascertainment date for censoring, the associations between plaque severity with MACE by age group were similar. Natural language processing was used to extract results of CCTA, which we have previously shown to be highly accurate[19], however inaccuracies in a minority of cases is possible. We did not perform quantitative plaque analysis, FFR-CT, or evaluate for peri-coronary inflammation via the fat attenuation index. While these CCTA features may provide additional prognostic and diagnostic utility in older adults, they are not currently used in routine clinical practice due to availability, complexity, and cost. As such our results remain highly relevant to current practice where clinicians receive reports detailing the severity of CAD as well as plaque involvement by each vessel. We used the number of vessels with plaque to identify plaque extent and found a significant and step-wise association between this measure and MACE (Figure 3). Alternative plaque extent metrics such as segment involvement score were not clinically reported during the study period and therefore not available. Additional techniques to evaluate plaque extent should be studied in the future. Our study was retrospective, and therefore interventions including revascularization and the use of preventive therapies based on the results of CCTA may have attenuated longitudinal CV risk. However, in sensitivity analysis accounting for early revascularization, the findings were similar. Not all patients were referred for invasive coronary angiography, even those thought to have obstructive disease on CCTA, which is reflective of real-world clinical

practice whereby the choice for further testing may depend on non-imaging factors such as symptoms, patient preferences, and additional co-morbidities. As a result, the sensitivity and specificity of CCTA in older adults compared with an invasive gold standard cannot be determined in this study design. Finally, our study population was drawn from patients referred to two major urban academic medical centers in the United States, which may limit the generalizability of our findings to other clinical settings.

In summary, our results support the prognostic value of CCTA in both younger (age<65) and older (age≥65) individuals and highlight that the detection of plaque may be particularly informative in the young, while identification of obstructive CAD may be more prognostically relevant in the elderly. While the 2021 ACC/AHA chest pain guideline favors stress testing in older adults and CCTA in younger adults, our findings suggest that among individuals with no known CAD, older age alone should not exclude a patient for referral for CCTA. Our study did not directly compare anatomic and functional testing and supports the fact that a future prospective randomized clinical outcomes trial in this area is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CCTA	coronary computed tomography angiography
ICA	invasive coronary angiography
CAD	coronary artery disease
CAD-RADS	Coronary Artery Disease Reporting and Data System
MACE	major adverse cardiovascular events
MI	myocardial infarction
FFR-CT	fractional flow reserve computed tomography

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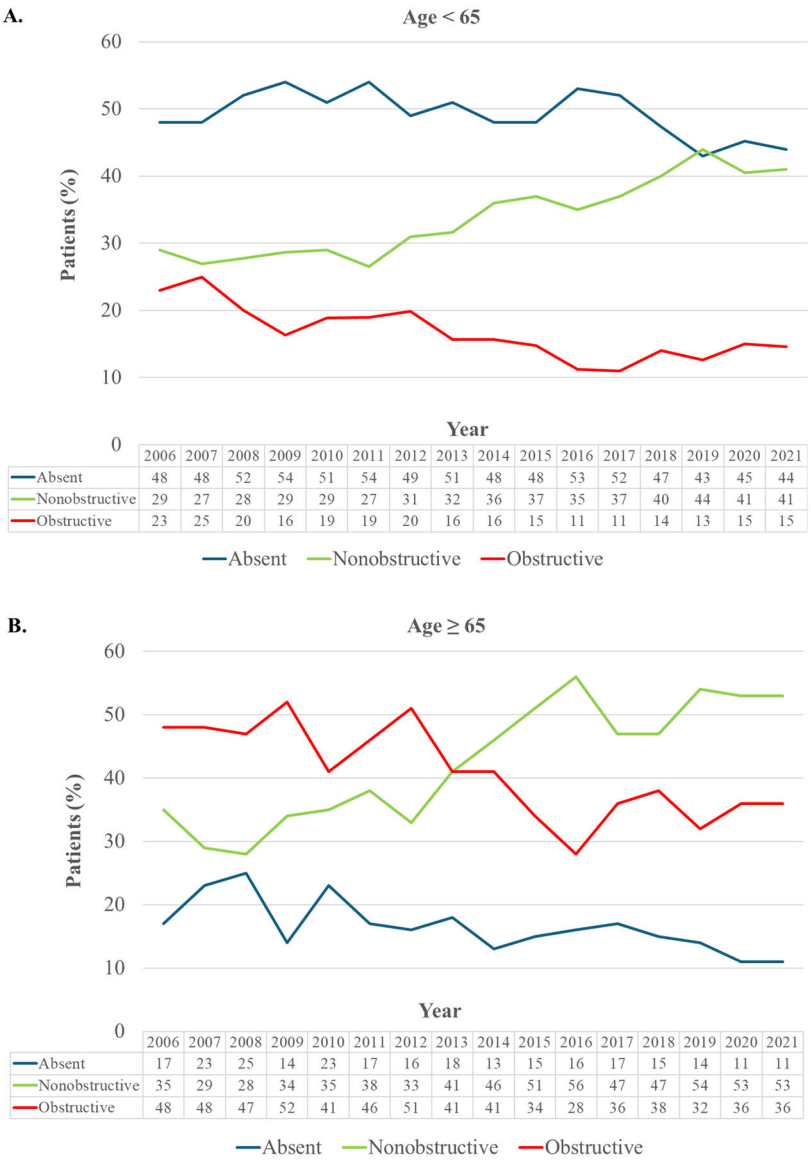


Age < 65	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Absent	48	48	52	54	51	54	49	51	48	48	53	52	47	43	45	44
Nonobstructive	29	27	28	29	29	27	31	32	36	37	35	37	40	44	41	41
Obstructive	23	25	20	16	19	19	20	16	16	15	11	11	14	13	15	15

Age ≥ 65	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Absent	17	23	25	14	23	17	16	18	13	15	16	17	15	14	11	11
Nonobstructive	35	29	28	34	35	38	33	41	46	51	56	47	47	54	53	53
Obstructive	48	48	47	52	41	46	51	41	41	34	28	36	38	32	36	36

Figure 1: Temporal Trends in CCTA Referrals Stratified by Age Group and Plaque Type

Rising prevalence of nonobstructive plaque and declining obstructive plaque among (A) younger and (B) older adults.

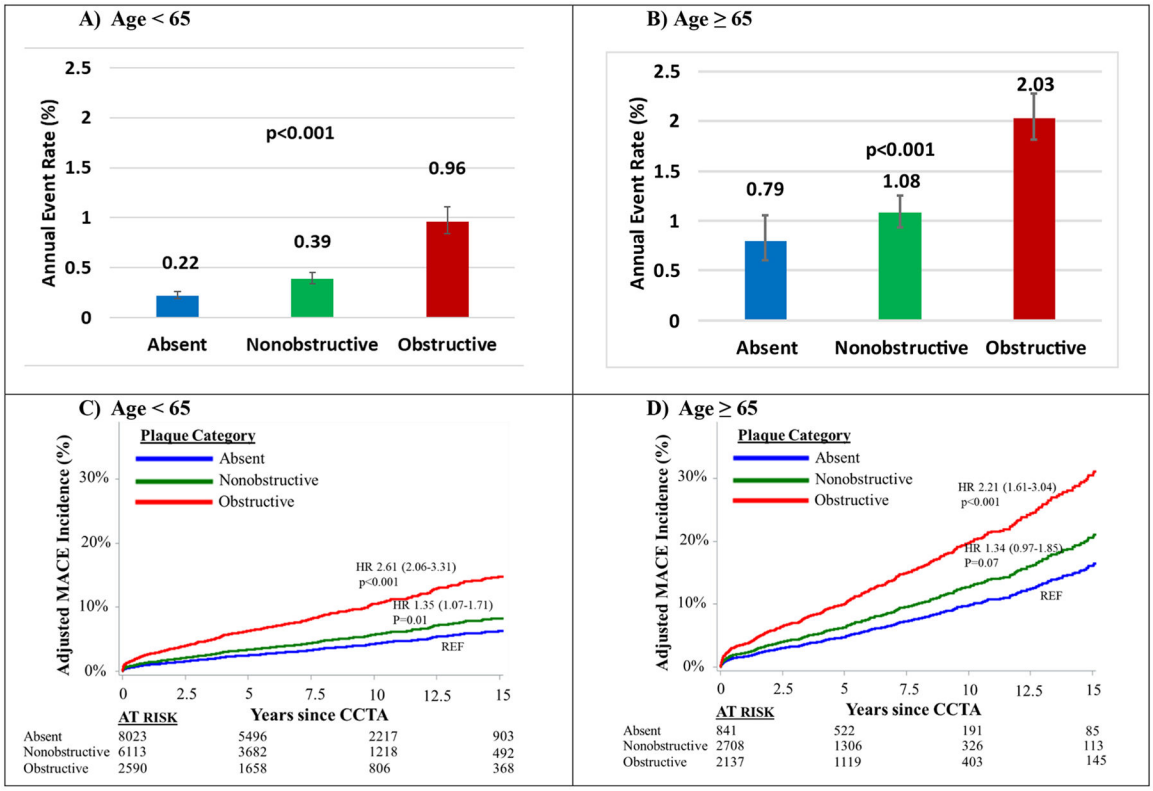
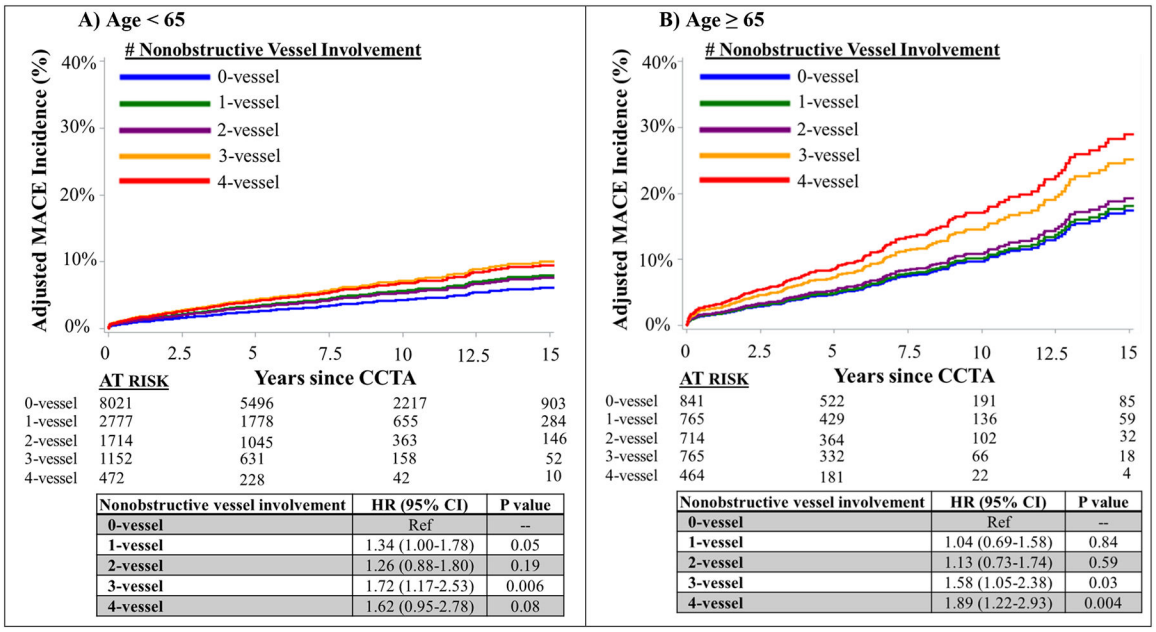


Figure 2: Adverse Cardiovascular Events Following CCTA, Stratified by Age Group and Plaque Severity

(A and B) Unadjusted annual incidence rates and (C and D) adjusted hazard for MACE (CV death, nonfatal MI, stroke). Adjusted for sex, hypertension, dyslipidemia, diabetes, morbid obesity, chronic kidney disease, current smoking, prior stroke or TIA, atrial fibrillation, baseline statin use, setting of test.



Nonobstructive vessel involvement	HR (95% CI)	P value
0-vessel	Ref	--
1-vessel	1.34 (1.00-1.78)	0.05
2-vessel	1.26 (0.88-1.80)	0.19
3-vessel	1.72 (1.17-2.53)	0.006
4-vessel	1.62 (0.95-2.78)	0.08

Nonobstructive vessel involvement	HR (95% CI)	P value
0-vessel	Ref	--
1-vessel	1.04 (0.69-1.58)	0.84
2-vessel	1.13 (0.73-1.74)	0.59
3-vessel	1.58 (1.05-2.38)	0.03
4-vessel	1.89 (1.22-2.93)	0.004

Figure 3: Adverse Cardiovascular Events Following CCTA Among Patients with Nonobstructive Plaque, Stratified by Age Group and Extent of Nonobstructive Plaque

Adjusted hazard for MACE (CV death, nonfatal MI, stroke) by age group and count of vessels (0–4) with nonobstructive plaque. Patients with obstructive plaque were excluded. Adjusted for sex, hypertension, dyslipidemia, diabetes, morbid obesity, chronic kidney disease, current smoking, prior stroke or TIA, atrial fibrillation, baseline statin use, setting of test.

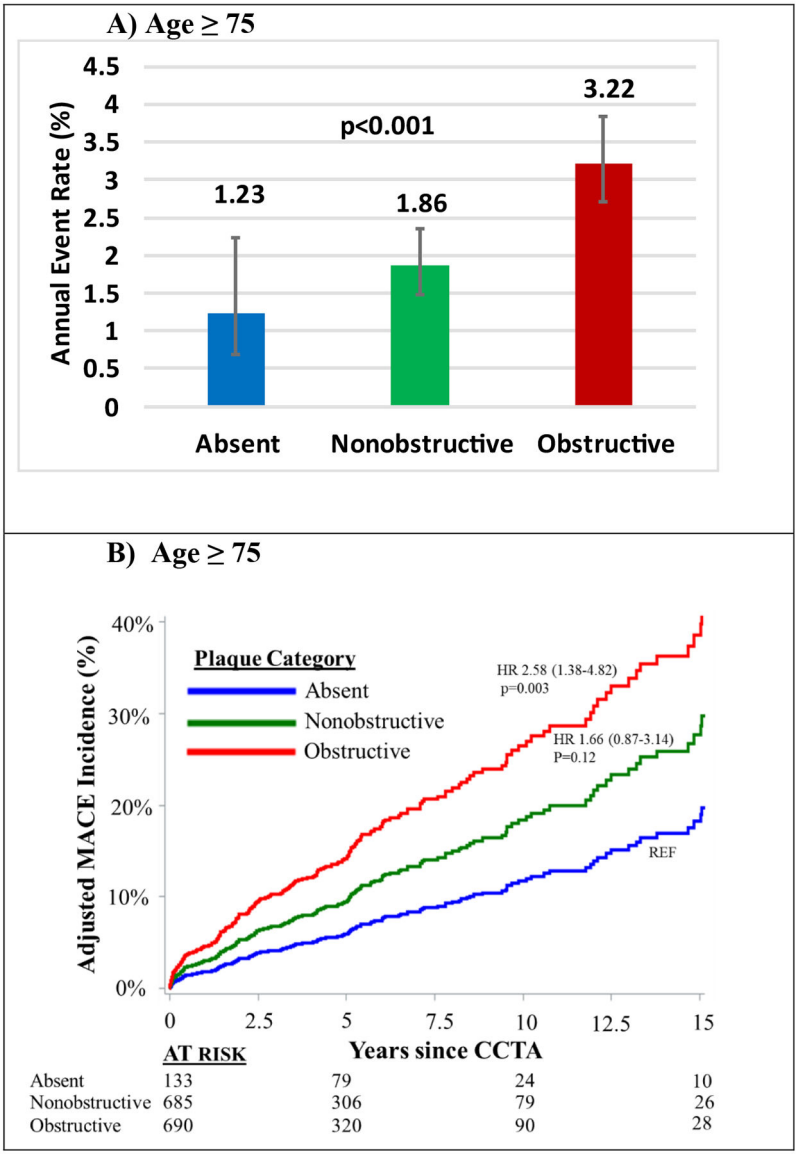


Figure 4: Adverse Cardiovascular Events Following CCTA Among Elderly, Stratified by Plaque Severity

(A) Unadjusted annual incidence rates and **(B)** adjusted hazard for MACE (CV death, nonfatal MI, stroke) by plaque group among those elderly defined as 75 and over. Adjusted for sex, hypertension, dyslipidemia, diabetes, morbid obesity, chronic kidney disease, current smoking, prior stroke or TIA, atrial fibrillation, baseline statin use, setting of test.

Table 1:

Baseline Characteristics, by Age Group

Characteristic	All Patients (n=22,412)	Age <65 (n=16,726, 74.6%)	Age ≥ 65 (n=5,686, 25.4%)	P value
Age	56 (47–65)	52 (45–58)	71 (68–75)	**<0.001**
Female	10,019 (45%)	7,007 (42%)	3,012 (53%)	**<0.001**
Race				**<0.001**
Non-Hispanic White	17,231 (77%)	12,412 (74%)	4,819 (85%)	
Non-Hispanic Black	1,528 (7%)	1,341 (8%)	187 (3%)	
Hispanic	631 (3%)	546 (3%)	85 (1%)	
Asian	816 (4%)	621 (4%)	195 (3%)	
Other	2,206 (10%)	1,806 (11%)	400 (7%)	
Hypertension	11,825 (53%)	7,873 (47%)	3,952 (70%)	**<0.001**
Diabetes	3,254 (15%)	2,237 (13%)	1,017 (18%)	**<0.001**
Dyslipidemia	10.639 (47%)	7,266 (43%)	3,373 (59%)	**<0.001**
Morbid obesity (BMI ≥ 40)	798 (4%)	653 (4%)	145 (3%)	**<0.001**
BMI, kg/m^2	28.3 (25.0–32.7); n=11,072	28.7 (25.1–33.3); n=7,949	27.7 (24.5–31.5); n=3,123	**<0.001**
CKD stage 3 or greater	1,139 (5%)	449 (3%)	690 (12%)	**<0.001**
ESRD	29 (0.1%)	20 (0.1%)	9 (0.2%)	0.48
Smoking Status				**<0.001**
Non-Smoker	14,135 (63%)	10,849 (65%)	3,286 (58%)	
Past Smoker	3,840 (18%)	2,331 (14%)	1,509 (27%)	
Current Smoker	3,788 (17%)	3,025 (19%)	763 (14%)	
CV Disease History				
Heart Failure	2,108 (9%)	1,315 (8%)	793 (14%)	**<0.001**
Stroke	889 (4.0%)	525 (3%)	364 (6%)	**<0.001**
TIA	708 (3%)	383 (2%)	325 (6%)	**<0.001**
Atrial Fibrillation	3,352 (15%)	1,838 (11%)	1,514 (27%)	**<0.001**
Lipid Lowering Therapy	8,836 (39%)	5,567 (33%)	3,269 (58%)	**<0.001**
Statin	8,635 (39%)	5,436 (33%)	3,199 (56%)	**<0.001**
Antiplatelets	8,422 (38%)	5,991 (36%)	2,431 (43%)	**<0.001**
Antihypertensive	16,258 (73%)	11,743 (70%)	4,515 (79%)	**<0.001**
Anticoagulants	1,967 (9%)	1,031 (6%)	936 (16%)	**<0.001**
Inpatient/Outpatient Status				**<0.001**
Outpatient	14.613 (65%)	10,489 (63%)	4,124 (73%)	
Inpatient	3,698 (17%)	2,738 (16%)	960 (17%)	
Outpatient – ER	4,043 (18.0%)	3,449 (21%)	594 (10%)	

Values are N (%) or median (Q1-Q3). CV = Cardiovascular; BMI = body mass index; CKD = chronic kidney disease; ESRD = end-stage renal disease; eGFR = estimated glomerular filtration rate by the CKD-EPI equation; TIA = transient ischemic attack; ER = emergency room

Table 2:

Plaque Findings on CCTA, by Age Group

Characteristic	All Patients (n=22,412)	Age <65 (n=16,726, 74.6%)	Age ≥ 65 (n=5,686, 25.4%)	P value
Presence of Plaque	13,548 (60%)	8,703 (52%)	4,845 (85%)	**<0.001**
≥ 1 nondiagnostic segments *	2,737 (12%)	1,864 (11%)	873 (15%)	**<0.001**
CAD-RADS Category				**<0.001**
0	8,864 (40%)	8,023 (48%)	841 (15%)	
1	3,218 (14%)	2,407 (14%)	811 (14%)	
2	5,603 (25%)	3,706 (22%)	1,897 (33%)	
3	1,585 (7%)	864 (5%)	721 (13%)	
4A	2,080 (9%)	1154 (7%)	926 (16%)	
4B	414 (2%)	192 (1%)	222 (4%)	
5	648 (3%)	380 (2%)	268 (5%)	
Plaque Category				**<0.001**
Absent (0%)	8,864 (40%)	8,023 (48%)	841 (15%)	
Nonobstructive (<50%)	8,821 (39%)	6,113 (37%)	2,708 (48%)	
Obstructive (50–100%)	4,727 (21%)	2,590 (15%)	2,137 (38%)	
CAC Score	2 (0–115); n=15,410	0 (0–40); n=11,487	125 (8–544); n=3,923	**<0.001**
Plaque Extent				**<0.001**
0 vessel	8,864 (40%)	8,023 (48%)	841 (15%)	
1 vessel	4,015 (18%)	3,154 (19%)	861 (15%)	
2 vessels	3,180 (14%)	2,193 (13%)	987 (17%)	
3 vessels	3,480 (16%)	2,033 (12%)	1,447 (25%)	
4 vessels	2,875 (13%)	1,325 (8%)	1,550 (27%)	

Values are N (%) or median (Q1-Q3). CAD-RADS = coronary artery disease reporting and data system; CAC = coronary artery calcium

* See supplementary table 3 for proportion by age group and study era

Table 3:

Hazard of primary outcome (CV death, acute MI, or stroke) by age group

A. Age < 65

Composite Outcome: MACE (CV death, nonfatal MI or stroke) (n=16,726)	**Event Rates**			
Plaque Group				
Absent	142/8,023 (1.8%)			
Nonobstructive	167/6,113 (2.7%)			
Obstructive	200/2,590 (7.7%)			
	Univariable		**Multivariable (n=16,676)**	
Characteristic	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Plaque Group				
Absent	Ref	--	Ref	--
Nonobstructive	1.73 (1.38–2.16)	**<0.001**	1.35 (1.07–1.71)	**0.01**
Obstructive	4.33 (3.49–5.37)	**<0.001**	2.61 (2.06–3.31)	**<0.001**
Female Sex			0.83 (0.68–1.01)	**0.06**
Hypertension			1.25 (1.01–1.53)	**0.04**
Dyslipidemia			1.28 (1.01–1.63)	**0.04**
Diabetes			1.97 (1.60–2.42)	**<0.001**
Chronic Kidney Disease			2.27 (1.67–3.09)	**<0.001**
Current Smoker			1.58 (1.30–1.91)	**<0.001**
Morbid Obesity (BMI ≥ 40)			1.20 (0.84–1.72)	0.32
Prior Stroke or TIA			1.61 (1.21–2.14)	**0.001**
Atrial fibrillation			2.30 (1.86–2.83)	**<0.001**
Baseline statin use			0.96 (0.77–1.20)	0.72
Setting				
Outpatient			Ref	--
Emergency			0.73 (0.52–1.04)	**0.08**
Inpatient			2.05 (1.68–2.49)	**<0.001**

B. Age ≥ 65

Composite Outcome: MACE (CV death, nonfatal MI or stroke) (n=5,686)	**Event Rates**			
Plaque Group				
Absent	48/841 (5.7%)			
Nonobstructive	173/2,708 (6.4%)			
Obstructive	279/2,137 (13.1%)			
	Univariable		**Multivariable (n=5,684)**	
Characteristic	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Plaque Group				
Absent	Ref	--	Ref	--
Nonobstructive	1.38 (1.00–1.90)	**0.048**	1.34 (0.97–1.85)	0.07

Obstructive	2.57 (1.89–3.49)	**<0.001**	2.21 (1.61–3.04)	**<0.001**
Female Sex			1.11 (0.92–1.33)	0.28
Hypertension			1.19 (0.94–1.51)	0.15
Dyslipidemia			1.28 (1.00–1.64)	0.05
Diabetes			1.63 (1.33–2.01)	**<0.001**
CKD (stage 3 or greater)			2.13 (1.73–2.62)	**<0.001**
Current Smoker			1.28 (1.01–1.61)	**0.04**
Morbid Obesity (BMI ≥ 40)			1.37 (0.86–2.18)	0.18
Prior stroke or TIA			1.84 (1.45–2.32)	**<0.001**
Atrial fibrillation			1.58 (1.31–1.91)	**<0.001**
Baseline statin use			0.70 (0.56–0.88)	**0.002**
Setting				
Outpatient			Ref	--
Emergency			0.53 (0.33–0.88)	**0.01**
Inpatient			1.73 (1.41–2.12)	**<0.001**

CV = cardiovascular; MI = myocardial infarction; CI = confidence interval; CKD = chronic kidney disease; BMI = body mass index; TIA = transient ischemic attack

Table 4:

Early outcomes – Invasive coronary angiography, PCI, and CABG proportion within 90 days after CCTA by age group and plaque group

Early Outcome after CCTA	Total	By Plaque Group			
		Absent	Nonobstructive	Obstructive	P value
Age < 65	N=16,726	N=8,023	N=6,113	N=2,590	
Early Invasive Coronary Angiography	1167 (7.0%)	60 (0.8%)	109 (1.8%)	998 (38.5%)	<0.001
Obstructive CAD on early ICA	829 (5.0%)	4 (0.04%)	31 (0.5%)	794 (31%)	<0.001
Early PCI	400 (2.4%)	3 (0.04%)	9 (0.1%)	388 (15.0%)	<0.001
Early CABG	173 (1.5%)	1 (0.01%)	5 (0.08%)	167 (6.4%)	<0.001
Age ≥ 65	N=5,686	N=841	N=2,708	N=2,137	
Early Invasive Coronary Angiography	869 (15.3%)	12 (1.4%)	51 (1.8%)	806 (37.7%)	<0.001
Obstructive CAD on ICA	658 (11.6%)	4 (0.5%)	9 (0.3%)	645 (30.2%)	<0.001
Early PCI	244 (4.3%)	2 (0.2%)	2 (0.1%)	244 (11.5%)	<0.001
Early CABG	211 (3.7%)	0 (0%)	0 (0%)	146 (6.8%)	<0.001

Values are N (%). PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CAD = coronary artery disease; ICA = invasive coronary angiography