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Research paper

Comparison of coronary atherosclerotic plaque progression in East Asians and Caucasians by serial coronary computed tomographic angiography: A PARADIGM substudy

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ABSTRACT

Objectives: To investigate potential differences in plaque progression (PP) between in East Asians and Caucasians as well as to determine clinical predictors of PP in East Asians.

Background: Studies have demonstrated differences in cardiovascular risk factors as well as plaque burden and progression across different ethnic groups.

Methods: The study comprised 955 East Asians (age 60.4 ± 9.3 years, 50.9% males) and 279 Caucasians (age 60.4 ± 8.6 years, 74.5% males) who underwent two serial coronary computed tomography angiography (CCTA) studies over a period of at least 24 months. Patients were enrolled and analyzed from the PARADIGM (*P*rogression of *A*the*R*osclerotic Pl*A*que *D*eterm*I*ned by Computed Tomo*G*raphic Angiography I*M*aging) registry. After

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propensity-score matching, plaque composition and progression were compared between East Asian and Caucasian patients. Within East Asians, the plaque progression group (defined as plaque volume at follow-up CCTA minus plaque volume at baseline CCTA> 0) was compared to the no PP group to determine clinical predictors for PP in East Asians.

Results: In the matched cohort, baseline volumes of total plaque as well as all plaque subtypes were comparable. There was a trend towards increased annualized plaque progression among East Asians compared to Caucasians (18.3 ± 24.7 mm^3/year vs 16.6 mm^3/year, p = 0.054). Among East Asians, 736 (77%) had PP. East Asians with PP had more clinical risk factors and higher plaque burden at baseline (normalized total plaque volume of144.9 ± 233.3 mm^3 vs 36.6 ± 84.2 mm^3 for PP and no PP, respectively, p < 0.001). Multivariate logistic regression analysis showed that baseline normalized plaque volume (OR: 1.10, CI: 1.10–1.30, p < 0.001), age (OR: 1.02, CI: 1.00–1.04, p = 0.023) and body mass index (OR: 2.24, CI: 1.01–1.13, p = 0.024) were all predictors of PP in East Asians. Clinical events, driven mainly by percutaneous coronary intervention, were higher among the PP group with a total of 124 (16.8%) events compared to 22 (10.0%) in the no PP group (p = 0.014).

Conclusion: East Asians and Caucasians had comparable plaque composition and progression. Among East Asians, the PP group had a higher baseline plaque burden which was associated with greater PP and increased clinical events.

Abbreviations

ACS	Acute Coronary Syndrome
BMI	Body Mass Index
CAD	Coronary Artery Disease
CCTA	Coronary Computed Tomography Angiography
HU	Hounsfield Unit
LDL	Low-Density Lipoprotein
HDL	High-Density Lipoprotein
MACE	Major Adverse Cardiac Event(s)
PARADIGM	*P*rogression of *A*the*R*osclerotic Pl*A*que *D*eterm*I*ned by Computed Tomo*G*raphic Angiography I*M*aging
PP	Plaque Progression
CABG	Coronary Artery Bypass Grafts
MI	Myocardial Infraction
PCI	Percutaneous Coronary Intervention

1. Introduction

East Asian populations have a lower risk for coronary artery disease (CAD), myocardial infarction (MI), recurrent MI and cardiovascular mortality.[1–4] Jiang et al.[5] reported that ethnically Caucasian Australian individuals typically develop coronary artery lesions 10 years earlier than ethnically Chinese individuals. The potential explanations for this observation include genetic variation and differences in the prevalence of risk factors responsible for diverse mechanisms of plaque formation, erosion, rupture or thrombosis.[2,6] In a recent coronary computed tomography angiography (CCTA) analysis of non-calcified plaque among Caucasian and East Asian patients with suspected coronary artery disease, East Asians' plaque comprised less high risk (fibrofatty and necrotic core) plaque and more low risk (fibrous) plaque.[1]

Although prior reports have indicated that East Asians have a lower burden of atherosclerosis compared to other ethnic groups,[5,7,8] no studies have compared atherosclerotic plaque progression and its composition after matching such patients for baseline clinical risk factors, medication use, CCTA time interval as well as total and subtypes of normalized plaque volumes. Furthermore, there is no data evaluating coronary atherosclerotic plaque progression (PP) in East Asians. Thus, we aimed to 1) investigate changes in plaque morphology and composition as measured by serial CCTA in East Asian patients compared with matched Caucasian patients and (2) assess the predictors, rate and pattern of PP within East Asian patients.

2. Methods

2.1. Study population

The PARADIGM (*P*rogression of *A*the*R*osclerotic Pl*A*que *D*eterm*I*ned by Computed Tomo*G*raphic Angiography I*M*aging) registry (NCT02803411; ClinicalTrials.gov) was designed to identify serial changes in coronary atherosclerotic plaques over time. The methodology of the PARADIGM registry has been described in detail previously.[9] Briefly, PARADIGM is a prospective, international, multicenter, observational registry in which clinical, procedural, and follow-up data was collected on patients undergoing serial CCTA at interval of two or more years between 2003 and 2015. The 15 enrolling sites from seven countries were selected to represent medical centers of different sizes, diagnostic capabilities and to recruit patient populations with diverse clinical and demographic backgrounds. The study protocol was approved by the institutional review boards at all participating sites. For the present analysis, we excluded patients with ethnicities other than Caucasian or East Asian (n = 129), noninterpretable CCTA scans (n = 471), history of CAD (n = 175) as quantitative plaque analysis cannot be performed in revascularized segments, incomplete statin data (n = 159) as well as patients who stopped taking statins (n = 84) after their baseline CCTA scan, given the influence of statin treatment on changes in plaque morphology and composition (Fig. 1).[10–12]

2.2. CCTA interpretation

All CCTA acquisition, postprocessing and interpretation was in direct accordance with the Society of Cardiovascular Computed Tomography guidelines.[13,14] All datasets from each contributing center were transferred to an offline workstation for blinded analysis at a single core laboratory. Coronary atherosclerosis evaluation was performed on multiplanar and cross-sectional images by Level III-experienced readers masked to clinical results using semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9.1; Medis Medical Imaging Systems, Leiden, the Netherlands).[15] Segments with a diameter ≥2 mm were evaluated using a modified 17-segment American Heart Association model for coronary segment classification.[16] Total length of the analyzed coronary arteries for each patient and mean total analyzed vessels length of the study population was documented at baseline and follow up CCTA. The presence of atherosclerosis was defined as any tissue structure >1 mm^2 either within or adjacent to the lumen of the coronary artery, that could be discriminated from surrounding pericardial tissue, epicardial fat or the vessel lumen itself.[17] Compositional analysis was performed on all atherosclerotic plaques, using Hounsfield units (HU) cut-off values of: −30 to 30 HU for necrotic core; 31 to 130HU for fibrofatty plaque; 131 to 350HU for fibrous plaque; and ≥350HU for

calcified plaque.[18,19] For each patient, total vessel volume, plaque volume and its components (fibrous plaque volume, fibrofatty plaque volume, necrotic core plaque volume and calcified plaque volume) was reported at baseline and follow-up CCTA for longitudinal analysis. All plaque volume parameters were normalized to coronary artery length using the following formula: [(absolute plaque volume/total length of analyzed coronary arteries) x mean total analyzed vessel length of the study population].[20] The annual progression rate for normalized plaque volumes for each plaque type were calculated as follows: [(value of normalized plaque volume at follow-up CCTA - value of normalized plaque volume at baseline CCTA)/interscan interval)]. For comparison of East Asian patients with or without PP, we defined PP as follows: (plaque volume at follow-up - CCTA-plaque volume at baseline CCTA) > 0.[21]

2.3. Clinical endpoints

Major adverse cardiac events (MACE) among East Asians were documented; coronary artery bypass grafts (CABG), MI, percutaneous coronary intervention (PCI) and all-cause mortality.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), and categorical variables were presented as absolute counts and percentages. Between group differences were analyzed using the chi-square test for categorical variables, and those between continuous variables using Student's t-test or Mann-Whitney *U* test. Changes between baseline and follow-up CCTAs were analyzed using McNemar's test for categorical variables and paired Student's t-test for continuous variables.

We adjusted for confounding factors using propensity score matching in order to reduce the impact of differences in baseline characteristics between the two ethnic groups on the study endpoints. The propensity scores were calculated for each of the patients using a logistic regression model that included age, sex, hypertension, diabetes mellitus, dyslipidaemia, smoking status, family history of coronary artery disease, aspirin use, statin use, CCTA scan interval, and normalized plaque volume at baseline for all plaque subtypes (fibrofatty, fibrous, necrotic core and calcified plaque). The calibration ability and discrimination of the propensity score model were assessed by means of the Hosmer-Lemeshow

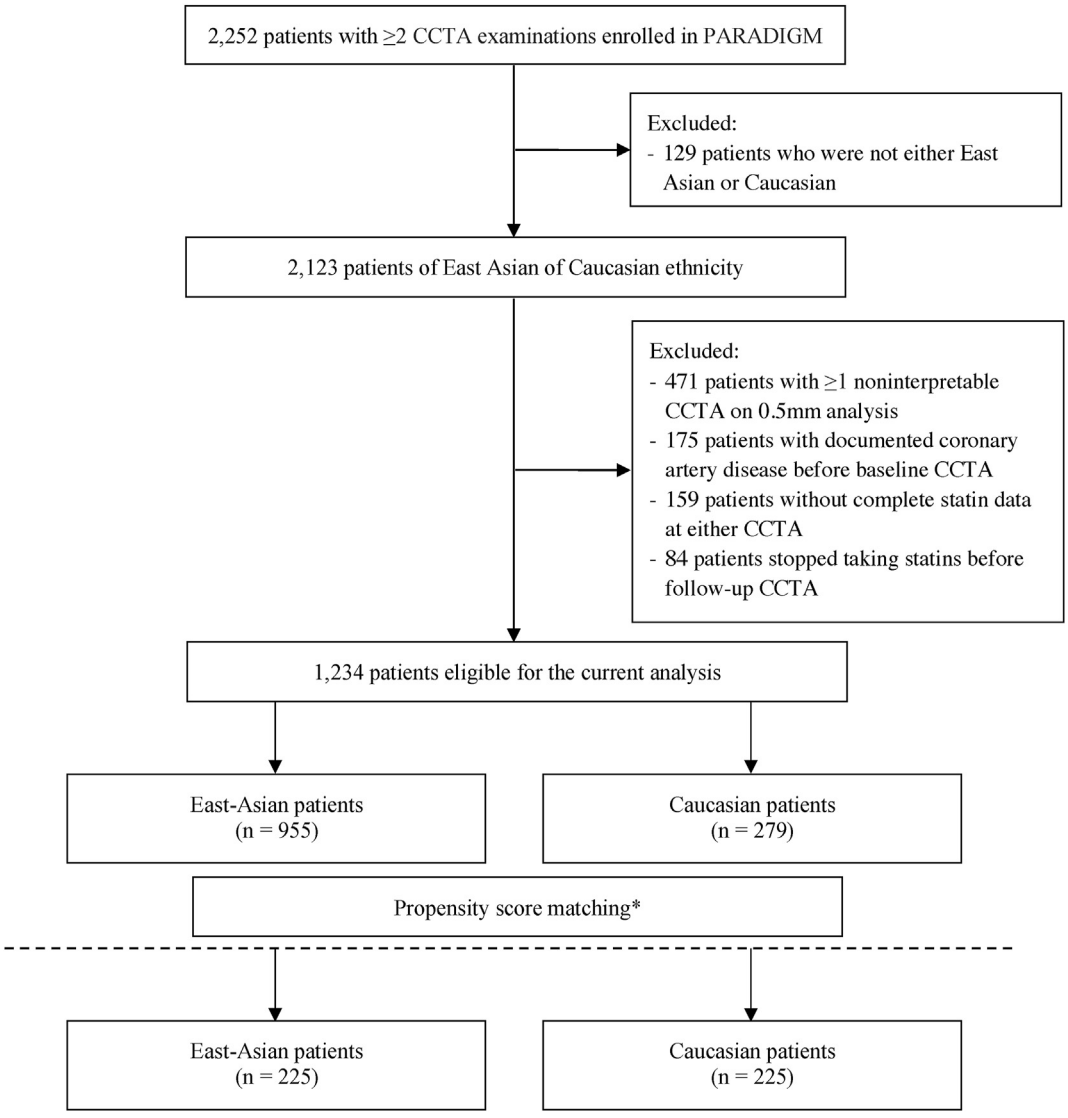

Fig. 1. Flowchart of the Study Population
* Factors that were included in the propensity score matching were age, sex, hypertension, diabetes mellitus, dyslipidaemia, smoking status, family history of coronary artery disease, aspirin use, statin use, CCTA scan interval, and normalized plaque volume at baseline for all plaque subtypes (fibrofatty, fibrous, necrotic core and calcified plaque).

goodness-of-fit test and Harrell's C-index. A p-value <0·05 was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS version 22 (IBM SPSS, Amronk, NY, USA), Stata (StataCorp, College Station, TX, USA) and R version 2.8.0 (R Development Core Team, Vienna, Austria).

3. Results

3.1. Study population

A total of 1,234 patients were eligible for the current analysis. Of these, 955 were East Asian and 279 were Caucasian (Fig. 1). Overall, the East Asian group had a significantly lower proportion of males, lower BMI and shorter interscan period. Incidence of hypertension, diabetes mellitus and smoking were more common among East Asians whereas dyslipidaemia and family history of CAD were less common ($p < 0.05$ for all). Significantly higher frequency use of aspirin with lower frequency use of beta-blocker and statin was noted in East Asian group. Lastly, significantly lower values of total cholesterol, LDL and HDL were also seen in East Asians (Table 1). The propensity score matched cohort comprised 225 patients in each group and the baseline characteristics are presented in Table 1.

3.2. Comparison of plaque composition and progression between East Asians and caucasians

3.2.1. Baseline plaque composition

Smaller baseline vessel volume was observed in East Asians compared to Caucasians. However, baseline volumes of total plaque as well as all four plaque subtypes were balanced between the East Asian and Caucasian groups in the matched cohort (Table 2).

3.2.2. Normalized plaque composition and progression

There were no differences between ethnic groups in normalized plaque volumes (total plaque and subtypes) at baseline and follow-up CCTA. Moreover, annualized progression was comparable though there was a trend towards higher annualized total plaque progression among East Asians compared to Caucasians (18.3 ± 24.7 mm^3/year vs 16.6 ± 29.2 mm^3/year, p = 0.054, Table 3). The compositional percentage of plaque progression of fibrous, fibrofatty, calcified and necrotic core plaque are presented in Fig. 2; no statistically significant differences between groups was observed.

Table 2
Baseline plaque characteristics.

Variable	Matched Cohort		
	East Asian (n = 225)	**Caucasian (n = 225)**	***p*-Value**
Total Vessels Volume, mm^3	2150.2 (1621.5–2893.3)	2417.9 (1660.6–3187.3)	**0.049**
Plaque Volumes			
Total Plaque Volume, mm^3	36.6 (0.0–133.7)	42.1 (0.0–107.9)	0.80
Fibrous Volume, mm^3	20.2 (0.0–59.3)	21.1 (0.0–55.9)	0.94
Fibrofatty Volume, mm^3	3.3 (0.0–16.5)	2.2 (0.0–14.0)	0.44
Necrotic Core Volume, mm^3	0.0 (0.0–0.7)	0.0 (0.0–0.5)	0.42
Calcified Volume, mm^3	3.4 (0.0–33.6)	5.9 (0.0–31.1)	0.55

3.3. Characterizing plaque progression in East Asians

3.3.1. Baseline characteristics

Within the East Asian group, 736 patients had PP whereas 219 had no PP (Table 4). Patients with PP were significantly older, had higher BMI and increased frequencies of hypertension, diabetes mellitus and dyslipidemia. Use of aspirin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and statins were higher in the PP group. The PP group also had significantly lower HDL level, and higher triglyceride level and HbA1C.

Table 1
Baseline characteristics.

Variable	Unmatched Cohort			Matched Cohort*		
	East Asian (n = 955)	Caucasian (n = 279)	*p*-Value	East Asian (n = 225)	Caucasian (n = 225)	*p*-Value
Demographics						
Age, years	60.4 ± 9.3	60.4 ± 8.6	0.88	60.1 ± 9.5	60.8 ± 8.6	0.42
Male sex, n (%)	486 (50.9)	208 (74.5)	<0.001	153 (68.0)	161 (71.6)	0.41
Clinical Characteristics and Medical History						
BMI, kg/m^2	24.8 ± 3.01	26.5 ± 3.5	<0.001	26.2 ± 3.3	26.2 ± 3.3	0.93
Hypertension, n (%)	540 (56.7)	103 (37.1)	<0.001	97 (43.5)	92 (41.1)	0.60
Diabetes Mellitus, n (%)	238 (24.9)	19 (6.8)	<0.001	19 (8.4)	17 (7.6)	0.72
Dyslipidemia, n (%)	271 (28.4)	161 (57.9)	<0.001	109 (48.9)	115 (51.3)	0.60
Family History of CAD, n (%)	237 (24.8)	93 (33.3)	0.005	70 (31.1)	69 (30.7)	0.92
Current Smoker, n (%)	178 (18.7)	36 (13)	0.03	29 (12.9)	27 (12.2)	0.80
Medications						
Aspirin, n (%)	396 (41.5)	76 (27.2)	<0.001	70 (31.1%)	67 (29.8%)	0.76
Beta-blocker, n (%)	235 (24.6)	107 (38.8)	<0.001	74 (36.1%)	73 (36.1%)	0.99
ACE inhibitor/ARB, n (%)	276 (28.9)	62 (22.8)	0.047	59 (26.2%)	54 (24.6%)	0.69
Statin, n (%)	577 (60.4)	192 (68.8)	0.01	154 (68.4%)	153 (68.0%)	0.92
Laboratory Data						
Total cholesterol, mg/dL	185.9 ± 38.2	210.9 ± 42.8	<0.001	188.4 ± 38.7	210.6 ± 42.0	**<0.001**
LDL, mg/dL	114.3 ± 34.6	123.2 ± 35.2	<0.001	117.9 ± 36.2	123.4 ± 33.9	0.13
HDL, mg/dL	49.3 ± 12.5	57.7 ± 18.1	<0.001	49.4 ± 12.3	57.9 ± 18.6	**<0.001**
Triglycerides, mg/dL	146.4 ± 84.9	149.2 ± 103.1	0.67	148.5 ± 77.9	148.6 ± 106.5	0.99
Creatinine, mg/dL	1.0 ± 0.7	1.0 ± 0.2	0.42	1.1 ± 0.9	1.0 ± 0.2	0.41
Interscan period, years	3.6 ± 1.4	4.7 ± 1.9	<0.001	4.3 ± 1.6	4.4 ± 1.8	0.40

BMI – Body mass index, CAD - Coronary artery disease, ACE – Angiotensin converting enzyme, ARB – Angiotensin II receptor blocker, LDL – Low density lipoprotein, HDL – high density lipoprotein.
*Factors that were included in the propensity score matching were age, sex, hypertension, diabetes mellitus, dyslipidaemia, smoking status, family history of coronary artery disease, aspirin use, statin use, CCTA scan interval, and normalized plaque volume at baseline for all plaque subtypes (fibrofatty, fibrous, necrotic core and calcified plaque).

Table 3
Normalized plaque volumes and progression in East Asians and Caucasians.

Variable	Matched Cohort		
	East Asian (n = 225)	Caucasian (n = 225)	*p*-Value
Total plaque volume			
Baseline CCTA, mm^3	110.4 ± 192.4	111.7 ± 246.8	0.92
Follow-up CCTA, mm^3	185.0 ± 278.4	172.7 ± 316.4	0.31
Annualized Progression, mm^3/year	18.3 ± 24.7	16.6 ± 29.2	0.054
Fibrous volume			
Baseline CCTA, mm^3	49.0 ± 89.0	49.1 ± 98.1	0.82
Follow-up CCTA, mm^3	70.8 ± 103.9	70.3 ± 120.5	0.31
Annualized Progression, mm^3/year	5.1 ± 11.3	5.5 ± 13.0	0.11
Fibrofatty volume			
Baseline CCTA, mm^3	14.3 ± 23.4	15.3 ± 33.7	0.50
Follow-up CCTA, mm^3	20.1 ± 34.0	24.2 ± 56.6	0.66
Annualized Progression, mm^3/year	1.5 ± 7.9	2.4 ± 10.0	0.23
Necrotic core volume			
Baseline CCTA, mm^3	1.1 ± 2.5	1.3 ± 3.5	0.41
Follow-up CCTA, mm^3	2.2 ± 6.0	2.0 ± 5.3	0.63
Annualized Progression, mm^3/year	0.3 ± 1.5	0.2 ± 1.1	0.18
Calcified volume			
Baseline CCTA, mm^3	46.0 ± 100.0	46.1 ± 137.2	0.48
Follow-up CCTA, mm^3	92.1 ± 183.2	75.3 ± 183.3	0.99
Annualized Progression, mm^3/year	11.4 ± 22.0	8.3 ± 18.4	0.27

CCTA - Coronary computed tomography angiography.

3.3.2. Comparison of plaque composition and progression

Compared to East Asians without PP, the PP group had statistically significantly higher baseline volumes for all plaque subtypes except for necrotic core. The PP group demonstrated statistically significantly higher rates of annualized PP for all four plaque subtypes (Table 5).

3.3.3. Clinical predictors of plaque progression

Univariate logistic regression analysis revealed that age, BMI, hypertension, dyslipidemia, diabetes mellitus and statin treatment were associated with PP in the East Asian group. In multivariate logistic regression analysis, age, BMI, dyslipidemia, diabetes mellitus and statin use remained as risk factors for PP (Table 6). When the multivariate analysis was repeated with the additional parameter of baseline normalized total plaque volume per 10 mm^3, only age (OR: 1.02, CI: 1.00–1.04, p = 0.023), BMI (OR: 2.24, CI: 1.01–1.13, p = 0.024) and baseline normalized total plaque volume (OR: 1.10, CI: 1.10–1.30, p < 0.001) remained as clinical predictors for PP.

3.3.4. Clinical endpoints

The median clinical follow-up period was 8.5 [IQR: 6.4–9.6] years. There were a total of 124 (16.8%) MACE in the PP group compared to only 22 (10.0%) in the non-PP group (p = 0.014). PCI was the most

Table 4
Baseline characteristics of East Asians stratified by plaque progression.

	No PP (n = 219)	PP (n = 736)	*p*-Value
Demographics			
Age, years	57.5 ± 10.0	61.2 ± 9.0	**<0.001**
Male sex, n (%)	99 (45.2)	387 (52.6)	0.055
Clinical Characteristics and Medical History			
BMI, kg/m2	24.3 ± 3.3	25.0 ± 2.8	**0.005**
Hypertension, n (%)	97 (44.3)	443 (60.4)	**<0.001**
Diabetes Mellitus, n (%)	34 (15.5)	204 (27.8)	**<0.001**
Dyslipidemia, n (%)	43 (19.6)	228 (31.1)	**0.001**
Family History of CAD, n (%)	57 (26.0)	180 (24.5)	0.65
Current Smoker, n (%)	38 (17.4)	140 (19.1)	0.57
Medications			
Aspirin, n (%)	72 (32.9)	324 (44.0)	**0.003**
Beta-blocker	51 (23.3)	184 (25.0)	0.61
ACEi/ARB, n (%)	43 (19.6)	233 (31.7)	**0.001**
Statin, n (%)	103 (47.0)	474 (64.4)	**<0.001**
Laboratory Data			
HbA1C, %	6.2 ± 1.1	6.4 ± 1.2	**0.046**
Total cholesterol, mg/dL	186.5 ± 38.2	185.7 ± 38.2	0.79
LDL, mg/dL	115.5 ± 33.5	114.0 ± 35.0	0.58
HDL, mg/dL	51.1 ± 13.2	48.8 ± 12.2	**0.02**
Triglycerides, mg/dL	136.2 ± 80.5	149.0 ± 86	**0.04**
Creatinine, mg/dL	1.0 ± 0.5	1.0 ± 0.7	0.47
Interscan period, years	3.5 ± 2.3	3.6 ± 1.4	0.22

PP – Plaque progression, BMI – Body mass index, CAD - Coronary artery disease, ACE – Angiotensin converting enzyme, ARB – Angiotensin II receptor blocker, LDL – Low density lipoprotein, HDL – high density lipoprotein.

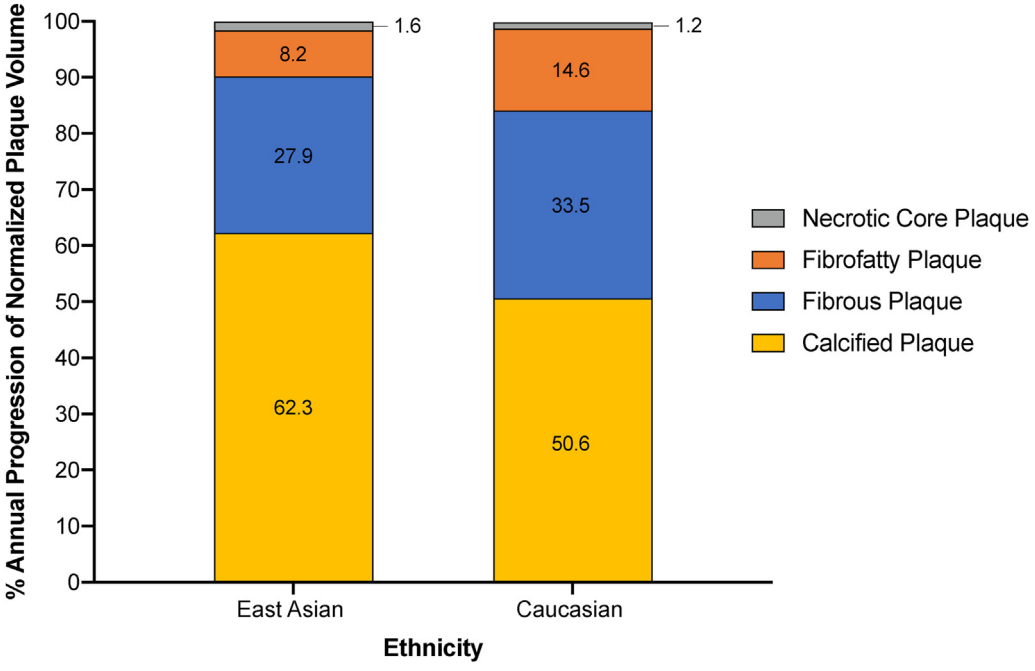

Fig. 2. Ethnic differences in compositional percentage of plaque progression.

Table 5
Changes in normalized plaque volumes in East Asians with or without plaque progression.

	No PP (n = 219)	PP (n = 736)	*p*-Value
Total plaque volume			
Baseline CCTA, mm^3	36.6 ± 84.2	144.9 ± 233.3	<0.001
Follow-up CCTA, mm^3	32.6 ± 77.5	227.7 ± 11.2	<0.001
Annualized progression, mm^3/year	−1.3 ± 3.3	23.6 ± 28.9	<0.001
Fibrous volume			
Baseline CCTA, mm^3	14.6 ± 33.5	64.0 ± 106.8	<0.001
Follow-up CCTA, mm^3	15.0 ± 37.6	90.2 ± 117. 7	<0.001
Annualized progression, mm^3/year	−0.1 ± 4.8	7.7 ± 16.4	<0.001
Fibrofatty volume			
Baseline CCTA, mm^3	12.6 ± 34.9	24.1 ± 39.3	<0.001
Follow-up CCTA, mm^3	6.0 ± 19.2	28.1 ± 46.3	<0.001
Annualized progression, mm^3/year	−2.0 ± 5.2	1.4 ± 9.7	<0.001
Necrotic core volume			
Baseline CCTA, mm^3	2.6 ± 8.7	2.6 ± 8.7	0.75
Follow-up CCTA, mm^3	0.9 ± 5.5	3.3 ± 8.5	<0.001
Annualized progression, mm^3/year	−0.5 ± 2.2	0.2 ± 2.2	<0.001
Calcified volume			
Baseline CCTA, mm^3	6.9 ± 24.9	54.1 ± 125.2	<0.001
Follow-up CCTA, mm^3	10.7 ± 33.4	106.2 ± 196.5	<0.001
Annualized progression, mm^3/year	1.2 ± 4.0	14.4 ± 24.7	<0.001

CCTA - Coronary computed tomography angiography.

Table 6
Independent clinical risk factors for plaque progression in East Asians.

Clinical Variable	Univariate		Multivariate	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Age, years	1.04 (1.03–1.06)	<0.001	1.04 (1.02–1.06)	<0.001
Male	1.34 (0.99–1.82)	0.056	1.52 (1.09–2.12)	0.013
BMI	1.09 (1.03–1.15)	0.002	1.08 (1.02–1.14)	0.007
Smoking	1.12 (0.75–1.66)	0.572		
Hypertension	1.91 (1.41–2.58)	<0.001	1.31 (0.93–1.84)	0.121
Dyslipidemia	1.84 (1.28–2.67)	0.001	1.52 (1.01–2.29)	0.043
Diabetes Mellitus	2.09 (1.40–3.12)	<0.001	1.63 (1.07–2.48)	0.022
LDL	0.99 (0.99–1.00)	0.580		
Statin Treatment	1.95 (1.40–2.73)	<0.001	1.47 (1.02–2.14)	0.040

BMI – Body mass index, LDL – Low density lipoprotein, OR – Odds ratio.

frequent event in both groups (Table 7). East Asian patients with MACE were older with higher prevalence of diabetes mellitus and hypertension. Baseline total plaque volume and its subtypes were higher among patients with MACE. However, the annualized plaque progression for patients with MACE was significantly higher only for total plaque and calcified plaque volume (Supplemental Data).

4. Discussion

In the current study, we have shown that East Asians and Caucasians had a similar pattern of PP after propensity-score matching. Further, we have demonstrated that PP amongst East Asians is driven by age, BMI and baseline normalized plaque volume.

4.1. Comparison of plaque progression between East Asians and Caucasians

This is the first study to investigate ethnic differences in PP in a large population with low-to-intermediate risk CAD. This was feasible due to the longitudinal nature of the PARADIGM registry and the ability to measure plaque volume and subtypes of plaque volume in CCTA studies. Prior to propensity matching, there were significant differences in

Table 7
Major adverse cardiac events in East Asians stratified by plaque progression.

	No PP (n = 219)	PP (n = 736)	*p*-Value
Follow-up duration after 1st CCTA, years	8.7 (6.5–9.7)	8.5 (6.3–9.5)	0.22
MACE	22 (10.0)	124 (16.8)	**0.014**
PCI, n (%)	16 (7.3)	105 (14.3)	**0.007**
CABG, n (%)	3 (1.4)	9 (1.2)	0.86
MI, n (%)	1 (0.5)	1 (0.1)	0.36
All-cause mortality, n (%)	2 (1.0)	9 (1.2)	0.71

MACE – major adverse cardiac events, PCI – Percutaneous coronary intervention, CABG – Coronary artery bypass grafts, MI – Myocardial Infraction.

baseline cardiovascular risk factors, medications and laboratory data. This is unsurprising as previous studies investigating East Asian and Caucasian populations have demonstrated some differences in BMI, cardiovascular risk factors and plaque characteristics. A previous CCTA study[1] reported similar plaque burden among Caucasians and East Asians in a matched cohort (age, gender, BMI and diabetes mellitus) but less composition of high risk plaque among East Asians. Other angiographic, ultrasound and optical coherence tomography studies showed smaller vessel diameter and volume among East Asians, highlighting the importance of normalizing plaque volume while studying differences in plaque burden and progression between the two groups.[6,22] Given these prior findings and our aim to investigate differences in PP, we had to adjust for clinical and laboratory data as well as statin treatment, but in addition also to adjust for baseline normalized plaque volume and subtypes of plaque volume. This allowed us to be able to uniquely evaluate the potential relationship between PP and ethnicity. The similar patterns and rates of PP amongst East Asians and Caucasians suggest that, while CAD risk factors and frequency of plaque development and burden may vary between these two ethnic groups, when East Asians or Caucasians develop plaque, they have similar patterns and rates of PP.

4.2. Plaque progression in East Asians

As expected, East Asian patients with PP had more baseline cardiovascular risk factors,[23] and less favorable levels of HbA1C, triglycerides and HDL. As a result, a higher frequency of medical treatment, including statin treatment, was noted in PP group. Consistent with a prior analysis from PARADIGM, baseline normalized plaque volume was also a strong predictor of PP among East Asians.[23] Other CCTA and IVUS studies have shown that greater baseline plaque volumes lead to higher rates of PP, which is also associated with a higher incidence of clinical events, mainly PCI.[23–27] This was irrespective of the plaque composition of high or low risk plaque which can change over time.[24] The current analysis is consistent with those reports with a clear message that those with more plaque are more likely to exhibit plaque progression, and confirmed this same phenomenon in an East Asian population. Furthermore, after inclusion of baseline normalized plaque volume as a confounding factor in the multivariate analysis, we found that only age and BMI remained as statistically significant clinical predictors for PP. This finding further highlights the importance of total baseline plaque volume as a strong predictor for PP beyond the presence of traditional risk factors and independent of statin treatment which has been previously linked to less PP.[11,12,28,29]

4.3. Limitations

Our findings must be considered in the context of some important limitations. First, propensity score matching may not have captured all potential confounding factors. The laboratory data revealed higher HDL and total cholesterol among Caucasians in the matched cohort, which may have had a potential effect on plaque progression. Furthermore, although laboratory data was assessed at baseline and follow-up, detailed

information regarding changes in medication (including statin type and doses) and lifestyle factors was not recorded following initial CCTA. Second, most of the East Asian patients enrolled in the PARADIGM registry were South Koreans. This limits the generalizability of our results to all East Asians. Third, there may be differences in patterns and burden of coronary atherosclerosis between native and migrant East Asian populations due to epigenetic and environmental influences. We did not account for country of residence in our analysis.

5. Conclusions

Our analysis of a large international CCTA registry suggests that the natural history of atherosclerosis is similar between East Asians and Caucasians. Among East Asians, baseline normalized plaque volume, age and BMI are important clinical predictors for PP.

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Appendix A. Supplementary data

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