Comparison of Coronary Atherosclerotic Plaque Burden and Composition as Assessed on Coronary Computed Tomography Angiography in East Asian and European-Origin Caucasians

Abdul Rahman Ihdayhid, MBBS[a,1], Markus Goeller, MD[b,c,1], Damini Dey, PhD[c], Nitesh Nerlekar, MBBS[a], Grace Yap, MBBS[a], Udit Thakur, MBBS[a], Daniel Adams, MBBS[a], James Cameron, MBBS, PhD[a], Sujith Seneviratne, MBBS[a], Stephan Achenbach, MD, PhD[b], and Brian Ko, MBBS, PhD[a,*]

Recent evidence suggests plaque morphology evaluated on coronary computed tomography angiography has prognostic implications. East Asians have a lower prevalence of myocardial infarction and cardiovascular mortality compared with European-origin Caucasians. We aimed to compare coronary atherosclerotic burden and plaque composition in a matched cohort of Caucasian and East Asians patients with stable chest pain who underwent computed tomography angiography. Two-hundred symptomatic patients (age 58.8 ± 7.9, male 51%) were matched for age, gender, body mass index, and diabetes (100 each ethnic group). A blinded core-laboratory quantified calcified and noncalcified plaque (NCP) volume and burden. Components of NCP were differentiated by plaque hounsfield unit (HU) thresholds which defined high-risk necrotic core (−30 to 30HU), fibrofatty plaque (31 to 130HU); and low-risk fibrous plaque (131 to 350HU). Composition of NCP components was derived as (NCP component volume/total NCP volume) × 100%. Segment Involvement Score, percent diameter and area stenosis were comparable in both groups. Similarly, there was no difference in the volume and burden of total, calcified and NCP. Compared with Caucasians, East Asians demonstrated lower composition of plaque attenuation corresponding to necrotic core (3.5 vs 5.1%; p = 0.004) and fibrofatty plaque (29.6 vs 37.3%; p = 0.005), and higher fibrous plaque (65.7 vs 57.6%; p = 0.004). On multivariable analysis East Asian ethnicity was independently associated with lower composition of high-risk plaque after adjustment for risk factors and scan parameters. These findings were consistent in a propensity-matched sensitivity-analysis. In conclusion, based on this matched cohort, East Asian ethnicity is associated with significantly less composition of high-risk NCP (necrotic core and fibrofatty plaque) and a higher composition of low-risk fibrous plaque compared with Caucasians; which may confer a lower risk of cardiovascular events. **(Am J Cardiol 2019;124:1012−1019)**

Epidemiological studies have observed a lower incidence of coronary artery disease (CAD), myocardial infarction, and cardiovascular mortality in East Asian populations compared with Caucasians.[1−4] These findings are not entirely explained by differences in cardiovascular risk factors, therefore additional mechanisms may play a role in the development and sequelae of CAD between these 2 populous ethnic groups. The presence of lipid-rich coronary atherosclerosis is central to the development of plaque rupture and acute coronary syndrome (ACS).[5] Coronary computed tomography angiography allows for non-invasive evaluation of vessel wall plaque morphology and composition with high diagnostic accuracy and reproducibility compared with invasive reference standards.[6] A recent landmark study demonstrated the prognostic value of differentiating lipid rich coronary plaque from predominately fibrous plaque as assessed by CTA,[7] with the identification of necrotic core and fibrofatty plaque on the basis of differences in CT attenuation being an independent predictor for ACS.[7] Quantitative differences in plaque morphology between East Asian and European-origin Caucasians are unknown. Therefore, the aim of this study was to compare CTA-assessed coronary atherosclerotic burden and plaque composition in a matched cohort of symptomatic East Asian and Caucasian patients with stable CAD.

[a]Monash Cardiovascular Research Centre, Monash University and MonashHeart, Monash Health, Clayton, Victoria, Australia; [b]Friedrich Alexander University Erlangen Nürnberg (FAU), Faculty of Medicine, Department of Cardiology, Erlangen, Germany; and [c]Biomedical Imaging Research Institute, Cedars-Sinai Medical Center, Los Angeles, California. Manuscript received March 5, 2019; revised manuscript received and accepted June 13, 2019.

Funding: Dr Abdul Rahman Ihdayhid and Dr Nitesh Nerlekar are both supported by the National Health and Medical Research Council of Australia and National Heart Foundation Scholarships.

[1]Both authors contributed equally to this body of work.

See page 1018 for disclosure information.

*Corresponding author: Tel: +61 3 9594 6666; fax: +61 3 9594 6939.

E-mail address: brianshiuhangko@gmail.com (B. Ko).

https://doi.org/10.1016/j.amjcard.2019.06.020

Methods

Two-hundred patients who underwent clinically mandated CTA were retrospectively included (100 patients for each ethnic group). These patients were identified from a database of patients who underwent a CTA at a single tertiary hospital in Melbourne, Australia between 2008 and 2017. This study only included (1) symptomatic stable patients with suspected CAD, (2) patients with ethnicity confirmed by telephone interview, (3) patients for whom a corresponding match for age, gender, body mass index (BMI) and diabetes was available in both ethnic groups, and (4) patients who were able to provide informed consent. Exclusion criteria included (1) poor CTA image quality defined as severe motion artifacts, inadequate vessel opacification, and severe noise-related blurring, (2) presentation with ACS, (3) previous coronary intervention or cardiac surgery, (4) patients with an incomplete data set recorded in the medical records, and (5) those with parents of different ethnic origins.

Ethnicity was initially identified by using a combination of validated surname lists[8] in addition to commonly recognized surnames associated with the respective ethnic groups (Supplementary Table S1). We identified the first 100 East Asian patients who fulfilled the inclusion criteria and sequentially matched them by age, gender, BMI, and presence of diabetes with 100 Caucasian patients. Ethnicity was confirmed via phone interview with East Asian ethnicity defined as both parents being of Chinese, Japanese, Korean, Thai, Vietnamese, Cambodian, Indonesian, Malaysian, or Myanmarese origin. Caucasian ethnicity was defined as having both parents of European origin.

Patient demographics and cardiovascular risk factors (definitions in Data Supplement, Part I) were obtained via standardized patient questionnaires before CTA and validated with information in the hospital medical records. The study was approved by the institutional human research ethics committee, and all participants gave informed consent.

Patients who met the inclusion criteria were included for analysis. The CT imaging protocol is provided in the Data Supplement. In accordance with the 18 coronary segment model,[9] all segments >1.8 mm were first visually inspected for the presence of coronary artery plaque and assessed for stenosis severity by a single experienced independent reader (MG) at a blinded core laboratory (Cedars-Sinai Medical Center, Los Angeles, California). Visually identified coronary plaque was defined as the presence of a clearly defined tissue greater than 1 mm^2 associated with the coronary wall and obstructive CAD was defined as >50% luminal stenosis.[10] The segment involvement score was defined as the number of coronary segments containing any plaque.

Segments with evidence of coronary plaque were further analyzed using semiautomated software (AutoPlaque version 2.0, Cedars-Sinai Medical Center, Los Angeles, California; Supplementary Figure S1). CTA images were evaluated using transverse and multiplanar reconstruction. On the multiplanar reconstruction views, the luminal centerline was manually defined with 5 to 7 control points and a circular region of interest was placed in the aorta to define normal blood pool. The proximal and distal limits of the plaque were identified with automated vessel wall correction applied for minor adjustments to vessel wall outline. Atherosclerotic plaque was characterized as noncalcified plaque and calcified plaque, as previously described.[11] Noncalcified plaque was further characterized by plaque hounsfield unit (HU) into the following components: necrotic core (−30 to 30 HU), fibrofatty plaque (31 to 130 HU), and fibrous plaque (131 to 350 HU).[7,12] The presence of necrotic core or fibrofatty plaque was defined as a quantitative high-risk plaque (HRP) feature and fibrous plaque as a low-risk plaque feature.[7] Perlesion volumes of each plaque type and total plaque volume were calculated and measurements summarized on a perpatient level. Plaque burden was defined as the plaque volume normalized to the vessel volume of the analyzed coronary lesion (plaque volume/vessel volume) × 100%. Calcified and noncalcified plaque composition was determined by measuring the proportion (%) of each plaque component in reference to measurements of total plaque volume. The composition of NCP components was derived as (NCP component volume/total NCP volume) × 100%. Minimal luminal diameter was determined semiquantitatively at the region of maximal stenosis degree. Quantitative maximal diameter stenosis was calculated as the ratio of the narrowest luminal diameter and the mean of 2 nondiseased reference points with ≥50% defined as obstructive disease. The remodeling index was determined as the ratio between the cross-sectional vessel area at the site of most severe area of stenosis and the mean cross-section vessel area at the proximal normal reference point.

Categorical variables are provided as frequencies (percentages). Continuous variables are presented as mean ± SD or median with interquartile range according to their distribution. The Shapiro-Wilk test was used to assess normality of continuous variables. Continuous variables were compared with Student's *t* test and the Mann-Whitney *U* test according to normality. Plaque volumes, plaque burden, and plaque composition were not normally distributed by the Shapiro-Wilk test. A multivariate linear regression was performed to determine the relation between plaque composition with the variables in 2 models. Model 1 included East Asian ethnicity, conventional risk factors (age, male gender, BMI, hypertension, hyperlipidaemia, diabetes, hypercholesteremia, and active smoking), cholesterol levels (total, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglyceride), statin use, and tube voltage. Model 2 included only factors with an association with composition of necrotic core, fibrofatty plaque, fibrous plaque, and calcified plaque identified on univariate analysis ($p < 0.25$).[13] To further account for the influence of confounders; plaque characteristics and multivariate analysis were reassessed after patients were matched in a 1:1 manner using propensity score method (Data Supplement, Part II). Interobserver variability of total plaque, calcified plaque, and NCP volumes were assessed by a similarly experienced blinded reader (AI) using an intraclass correlation coefficient in a random sample of 25 patients. A 2-tailed p value <0.05 was considered statistically significant. Statistical analysis was performed using STATA-14 (StataCorp, College Station, Texas).

Results

Two-hundred patients (100 patients in each ethnic group) were matched for age, gender, BMI, and presence of diabetes,

of which 138 patients had evidence of coronary plaque on visually assessed CTA (69 in each ethnic group; Figure 1). Baseline demographics, visually assessed CTA stenosis severity, and scan parameters are summarized in Table 1. Across the entire cohort, East Asians and Caucasians were well matched for cardiovascular risk factors, statin use, and CAD severity. Caucasians had a higher body surface area (1.85 vs 1.75 m^2, p <0.001), higher incidence of smoking (21 vs 9%, p = 0.017) with East Asians demonstrating a lower total cholesterol level (4.8 vs 5.3 mmol/L, p = 0.011), and comparable levels of LDL and HDL cholesterol. In patients with coronary plaque on CTA, there were no differences in baseline demographics between East Asians and Caucasians, including total cholesterol, LDL, and HDL levels. There was a small significant difference in the tube voltage utilized for CTA acquisition between East Asians and Caucasians (107.0 vs 111.2 kV, p = 0.012).

All 138 patients with evidence of coronary plaque on visual CTA assessment underwent quantitative plaque analysis using semiautomated software. The interobserver intraclass correlation coefficient was excellent for total plaque (0.995; 95% confidence interval [CI] 0.989 to 0.998; p <0.0001), noncalcified plaque (0.991; 95% CI 0.979 to 0.996; p <0.0001), and calcified plaque volumes (0.997; 95% CI 0.994 to 0.999; p <0.0001). Quantitative differences in CAD burden are summarized in Table 2. Between East Asians and Caucasians there was no observed difference between SIS (p = 0.777), total plaque length (p = 0.890), and maximal diameter stenosis (34.4% vs 37.0%; p = 0.405).

Differences between East Asian and Caucasian plaque volumes, plaque burden and composition are summarized in Table 3. There was no significant difference in total plaque, calcified and noncalcified plaque volume, and burden between both ethnic groups. Similarly, the plaque burden of the individual components of noncalcified plaque (necrotic core, fibrofatty plaque, and fibrous plaque) was comparable between ethnic groups. Compared with Caucasians, East Asians demonstrated significantly less composition of plaque attenuation corresponding to quantitative HRP features of necrotic core (3.5% vs 5.1%; p = 0.004), fibrofatty plaque (29.6% vs 37.3%; p = 0.005), and a higher composition of low-risk fibrous plaque (65.7% vs 57.6%; p = 0.004) (Figure 2). Calcified plaque composition was nominally lower in East Asians, but this did not reach statistical significance (5.8% vs 7.4%; p = 0.054).

Univariate factors associated with the composition of necrotic core, fibrofatty plaque, fibrous plaque, and calcified plaque are summarized in Table 4. Only East Asian ethnicity, total cholesterol and LDL levels (for calcified plaque) were associated with differences in plaque composition. East Asian ethnicity was significantly associated with less composition of plaque attenuation corresponding to necrotic core (ß = −2.1; p = 0.005), fibrofatty plaque (ß = −6.40; p = 0.008), calcified plaque (ß = −8.4; p = 0.035), and a higher composition of fibrous plaque (ß = 8.5; p = 0.005). A multivariate analysis was performed on the basis of 2 models; (1) adjusting for age, male gender, conventional cardiovascular risk factors, BMI, cholesterol levels (total, LDL, HDL, and triglycerides), statin use, and tube voltage and (2) adjusting only for factors associated with plaque composition on univariate analysis (p <0.25; Table 5). On both models, East Asian ethnicity was independently associated with significantly less composition of plaque attenuation corresponding to necrotic core, fibrofatty, calcified plaque, and a higher

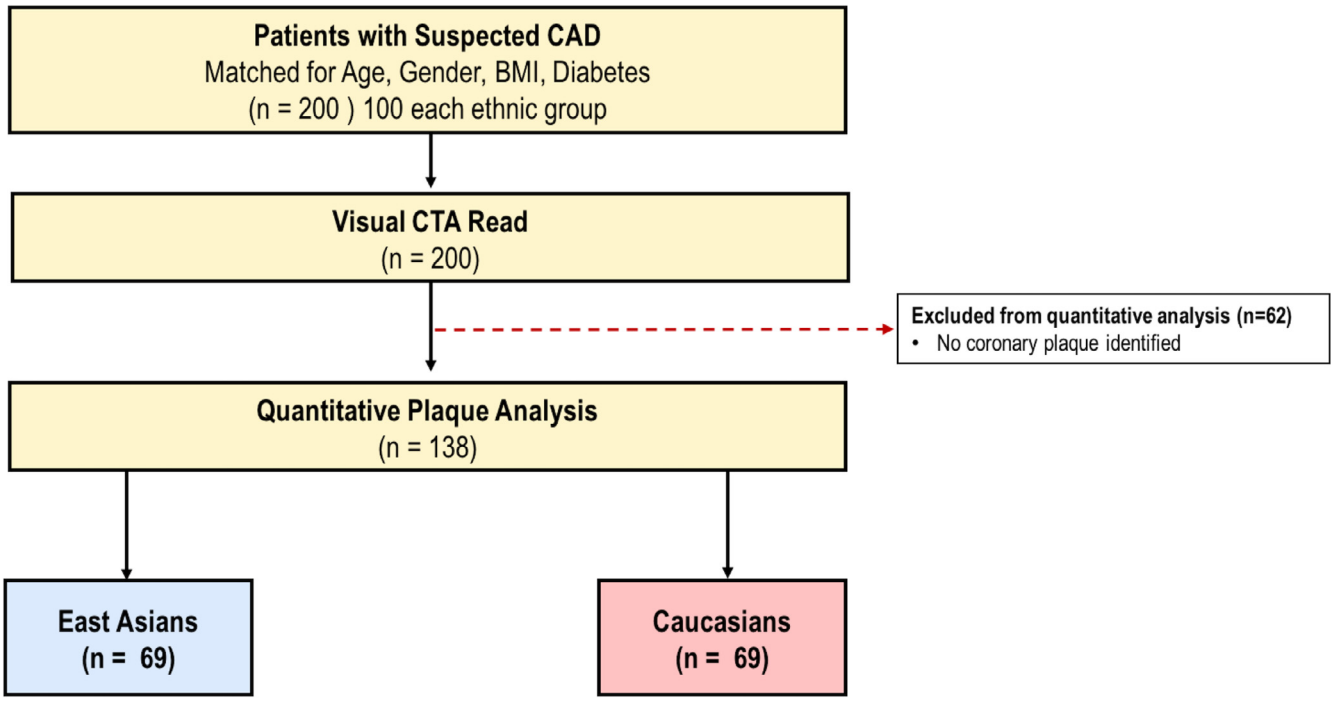

Figure 1. Study flow chart.

Table 1
Baseline demographics, coronary artery disease severity by visual assessment and CT acquisition characteristics for all patients and patients with coronary plaque

Variable	All patients			Patients with plaque		
	East Asians (n = 100)	Caucasians (n = 100)	p Value	East Asians (n = 69)	Caucasians (n = 69)	p Value
Age (years) (SD)	59.0 (7.9)	58.6 (8.0)	0.733	60.2 (7.4)	59.9 (7.4)	0.824
Men	51 (51%)	51 (51%)	1.0	41 (59)	43 (62)	0.727
Body mass index (kg/m^2)	25.6 (3.3)	26.2 (3.3)	0.183	25.8 (3.4)	26.0 (2.9)	0.645
Body surface area (m^2) (SD)	1.75 (0.2)	1.85 (0.2)	**<0.001***	1.78 (0.2)	1.87 (0.2)	**0.003***
Diabetes mellitus	25 (25%)	25 (25%)	1.0	23 (33)	20 (29)	0.581
Hypertension	54 (54%)	44 (44%)	0.157	45 (65)	34 (49)	0.058
Smoker	9 (9%)	21 (21%)	**0.017***	9 (13)	18 (26)	0.053
Hypercholesterolaemia	57 (57%)	63 (63%)	0.386	45 (65)	48 (79)	0.586
Total cholesterol (mg/dl) (SD)	86.4 (18.0)	95.4 (21.6)	**0.011***	86.4 (19.8)	93.6 (23.4)	0.100
Low density lipoprotein (mg/dl) (SD)	52.2 (16.2)	55.8 (19.8)	0.094	50.4 (17.6)	55.8 (19.8)	0.227
High density lipoprotein (mg/dl) (SD)	23.4 (6.7)	25.2 (8.3)	0.190	23.4 (7.0)	25.2 (8.8)	0.690
Triglycerides (mg/dl) (IQR)	23.4 (18.0-32.4)	23.4 (16.2-39.6)	0.742	23.4 (19.8-32.4)	27.0 (18.0-41.4)	0.553
Statin use	36 (36%)	33 (33%)	0.655	29 (42%)	28 (41%)	0.863
Coronary artery disease severity by visual assessment						
None	31 (31%)	31 (31%)	0.982	0	0	
Nonobstructive	49 (49%)	50 (50%)		49 (49%)	50 (50%)	0.850
No. of coronary arteries narrowed >50%	20 (20%)	19 (19%)	0.604	20 (20%)	19 (19%)	
1	14 (14%)	15 (15%)		14 (14%)	15 (15%)	
2	3 (3%)	3 (3%)		3 (3%)	3 (3%)	
3	3 (3%)	1 (1%)		3 (3%)	1 (1%)	
CT acquisition characteristics						
kV (SD)	106 (10)	110 (11)	**0.005***	107 (11)	111 (10)	**0.012***
mA (SD)	460 (194)	506 (182)	0.089	464 (184)	522 (184)	0.074
mSV (SD)	2.6 (1.6)	3.4 (1.8)	**0.001***	2.7 (1.7)	3.8 (1.9)	**<0.001***

Diabetes mellitus: fasting blood glucose > 126 mg/dl or requirement for insulin or oral hypoglycemic drugs. Hypertension: physician diagnosed with blood pressure > 140/90 mm Hg or therapy with antihypertensive medication. Hyperlipidemia: total serum cholesterol >99 mg/dl or therapy with lipid-lowering agent.

*Bold p values represent <0.05.

Table 2
Quantitative differences in coronary artery disease burden in patients with coronary plaque

Variable	East Asians (n = 69)	Caucasians (n = 69)	p Value
Segment involvement score			
Segments, (SD)	2.80 (2.5)	2.70 (1.6)	0.777
1-3	54 (78%)	49 (71%)	0.328
≥ 4	15 (22%)	20 (29%)	
CAD Severity by quantitative assessment			
Diameter stenosis %, (IQR)	34 (26-46)	37 (25-60)	0.405
Area stenosis %, (IQR)	55 (34-67)	59 (38-77)	0.182
Minimal luminal diameter mm, (SD)	2.4 (1.0)	2.1 (0.95)	0.103
Total plaque length mm, (IQR)	55 (23-104)	55 (22-100)	0.890
Remodeling index, (IQR)	1.6 (1.4-1.9)	1.7 (1.5-2.0)	0.222

composition of fibrous plaque. Triglyceride levels were associated with increasing fibrofatty and decreasing fibrous plaque composition.

These findings remained consistent when East Asian and Caucasian patients were further matched using propensity scores (Data Supplement, Table S3, Table S4). Multivariate analysis demonstrated that East Asians continued to be significantly associated with less composition of plaque attenuation corresponding to quantitative HRP features of necrotic core, fibrofatty plaque, and a higher composition of low-risk fibrous plaque.

Discussion

This study for the first time compares quantitative differences in atherosclerotic burden and plaque composition between East Asian and European-origin Caucasian populations as assessed by CTA. The main finding was that based on a matched cohort of patients with comparable overall plaque volume and burden, East Asians demonstrated a significantly lower composition of plaque attenuation corresponding to quantitative HRP features of necrotic core and fibrofatty plaque and a higher composition of low-risk

Table 3
Differences in plaque volume, burden, and composition between East Asians and Caucasians

Variable	East Asians (n = 69)	Caucasians (n = 69)	p Value
Plaque volume, mm^3 (IQR)			
Total plaque volume	189 (75-517)	248 (72-537)	0.764
Noncalcified plaque volume	158 (75-478)	213 (55-471)	0.821
Calcified plaque volume	10 (0-37)	17 (1.8-68)	0.151
Necrotic core volume	5.3 (1.3-25)	10 (2.0-24)	0.251
Fibrofatty volume	50 (21-170)	80 (18-170)	0.470
Fibrous volume	97 (38-260	123 (26-237)	0.738
Plaque burden, % (IQR)			
Total plaque burden	20 (13-31)	23 (12-32)	0.489
Noncalcified plaque burden	18 (11-26)	18 (10-29)	0.782
Calcified plaque burden	0.98 (0-3.1)	1.8 (0.3-4.5)	0.053
Necrotic core plaque burden	0.57 (0.2-1.2)	0.91 (0.3-1.1)	0.065
Fibrofatty plaque burden	4.7 (3.1-10.1)	6.9 (2.9-10.4)	0.190
Fibrous plaque burden	12 (6.2-17)	10 (5.7-17)	0.470
Plaque composition, % (IQR)			
Noncalcified plaque composition	94 (83-100.0)	93 (81-98)	0.054
Calcified plaque composition	5.8 (0-18)	7.4 (2.3-19)	0.054
Necrotic core plaque composition	3.5 (1.9-5.4)	5.1 (3.0-8.4)	**0.004***
Fibrofatty plaque composition	30 (23-39)	37 (28-45)	**0.005***
Fibrous composition	66 (54-76)	58 (46-67)	**0.004***

*Bold p values represent <0.05.

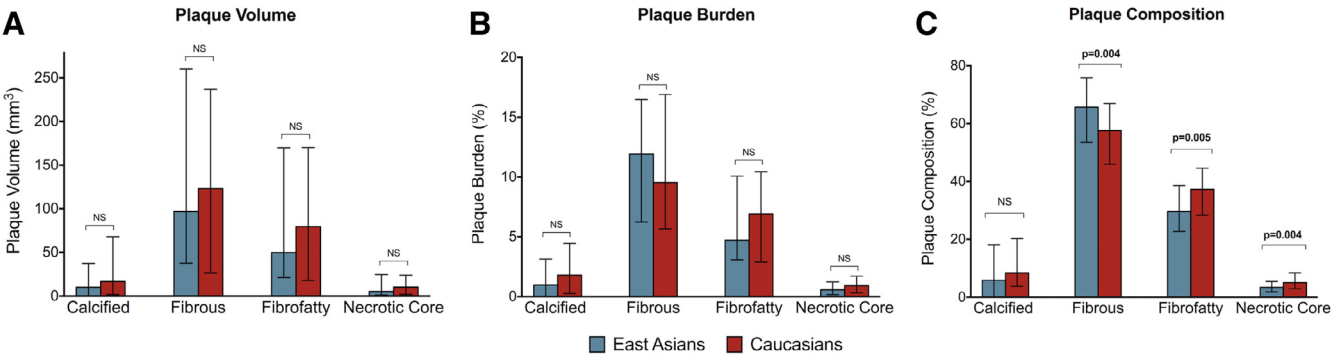

Figure 2. Differences in quantitative plaque volume, burden, and composition between East Asians and Caucasians. (*A* and *B*)demonstrate no difference in calcified plaque or components of noncalcified plaque volume and burden between East Asians and Caucasians. (*C*) East Asians demonstrate significantly less composition of high-risk quantitative plaque features of necrotic core and fibrofatty plaque and significantly more low-risk fibrous plaque compared with Caucasians. There was no difference in composition of calcified plaque. NS = not significant plaque burden (%) = (plaque volume/vessel volume) × 100 plaque composition (%): (calcified plaque volume/total plaque volume) × 100, (NCP component volume/total NCP volume) × 100.

fibrous plaque compared with Caucasians. The findings in this study are notable as both groups were well matched for cardiovascular risk factors, treatment with lipid-lowering medication as well as extent and severity of CAD.

Plaques with a lipid-rich necrotic core play an important role in the development of ACS in contrast to more stable fibrous plaque.[5] Recently, advances in image processing and software analysis permit accurate and detailed quantitative assessment of plaque composition and burden based on differences in attenuation on coronary CTA.[6] Clinical studies have demonstrated an increased risk of myocardial infarction[14] and cardiac death[15] in patients with a larger volume and relative composition of noncalcified and low-attenuation plaque. The recently published ICONIC study provided much needed insight into the prognostic value of CT-assessed plaque composition based on predefined HU thresholds.[7] Chang et al demonstrated that plaque composed of high-risk features of necrotic core and fibrofatty plaque was an independent predictor for patients who subsequently developed ACS, with no association for fibrous or calcified plaque.[7] Plaque composition was defined as plaque volume indexed to vessel volume (i.e., plaque burden), in contrast our study defined plaque composition as the relative proportion of each NCP component (necrotic core, fibrofatty, and fibrous plaque) to total NCP volume. The latter metric may provide insight into quantification of HRP features when disease burden and plaque volumes are comparable between study groups.

Several large population based studies have demonstrated a lower incidence of myocardial infarction and cardiovascular mortality in East Asians compared with Caucasians and South Asians, independent of traditional cardiovascular risk factors.[1–4] Our findings of East Asians being independently associated with a lower composition of necrotic core and

Table 4
Univariate factors associated with composition of necrotic core, fibrofatty plaque, fibrous plaque, and calcified plaque

	Necrotic core			Fibrofatty plaque			Fibrous plaque			Calcified plaque		
	ß	95% CI	P	ß	95% CI	P	ß	95% CI	P	ß	95% CI	P
East Asian ethnicity	−2.1	−3.6 to −0.7	**0.005***	−6.40	−11 to −1.7	**0.008***	8.5	2.7 to 14	**0.005***	−8.4	−16 to −0.6	**0.035***
Age	0.06	0 to 0.2	**0.228***	−0.1	−0.4 to 0.2	0.463	0.1	−0.4 to 0.5	0.777	0.1	−0.4 to 0.7	0.614
Male gender	−0.2	−1.8 to 1.4	0.780	1.2	−3.7 to 6.2	0.623	−1.0	−7.3 to 5.2	0.747	−0.6	−8.8 to 7.5	0.876
BMI	0.1	−0.2 to 0.3	0.627	0.59	−0.2 to 1.3	**0.128***	−0.6	−1.6 to 0.3	**0.181***	0.09	−1.2 to 1.4	0.893
BSA	1.2	−3.0 to 5.4	0.570	7.4	−6.0 to 21	0.277	−8.6	−25 to 8.1	0.311	8.0	−15 to 30	0.464
Hypertension	−0.5	−2.1 to 1.0	0.501	−3.2	−8.0 to 1.7	**0.202***	3.7	−2.4 to 9.8	**0.234***	4.2	−3.8 to 12	0.305
Diabetes	0.2	−1.4 to 1.8	0.802	−0.2	−5.4 to 5.0	0.949	−0.1	−6.5 to 6.5	0.990	−0.1	−8.6 to 8.5	0.996
Hypercholesteremia	1.2	−0.4 to 2.8	**0.137***	2.3	−2.8 to 7.4	0.374	−3.5	−9.9 to 2.9	0.278	1.2	−7.3 to 9.6	0.783
Total cholesterol	0.2	−0.4 to 0.9	0.488	0.7	−1.3 to 2.7	0.495	−0.9	−3.4 to 1.6	0.471	−3.3	−6.5 to −0.1	**0.043***
LDL-C	0.3	−0.5 to 1.0	0.509	0.8	−1.6 to 3.2	0.499	−1.1	−4.1 to 1.9	0.479	−4.1	−7.9 to −0.3	**0.035***
HDL-C	0.1	−1.6 to 1.8	0.906	−0.6	−6.1 to 4.9	0.835	0.48	−6.4 to 7.4	0.891	−3.9	−13 to 5.1	0.398
Triglycerides	0.45	−0.5 to 1.4	0.348	2.1	−0.9 to 5.1	**0.171***	−2.5	−6.3 to 1.2	**0.183***	−0.4	−5.3 to 4.4	0.868
Smoking	0.88	−1.1 to 2.8	0.374	5.6	−0.5 to 12	**0.070***	−6.5	−14 to 1.1	**0.094***	3.7	−6.3 to 14	0.465
Statin use	0.46	−1.1 to 2.0	0.559	1.3	−3.7 to 6.2	0.613	−1.7	−7.9 to 4.4	0.581	2.7	−5.4 to 11	0.513
kV	0.02	−0.05 to 0.1	0.642	0.1	−0.2 to 0.3	0.566	−0.1	−0.4 to 0.2	0.565	0.1	−0.2 to 0.5	0.433

ß − standardized regression coefficients.
* Bold p values represent <0.25.

Table 5
Multivariate analysis for association of East Asian ethnicity with composition of necrotic core, fibrofatty plaque, fibrous plaque, and calcified plaque

	Model 1			Model 2		
	ß coefficient	95% CI	p Value	ß coefficient	95% CI	p Value
Necrotic core	−1.9	−3.5 to −0.2	**0.025**	−2.1	−3.6 to −0.6	**0.006**
Fibrofatty plaque	−5.5	−11 to −0.4	**0.035**	−4.9	−9.8 to −0.1	**0.046**
Fibrous plaque	7.4	1.0 to 14	**0.024**	6.9	0.9 to 13	**0.026**
Calcified plaque	−9.3	−18 to 0.8	**0.033**	−9.6	−17 to −9.2	**0.016**

Model 1 − East Asian ethnicity, age, male gender, bmi, hypertension, diabetes, hypercholesteremia, total cholesterol, LDL-C level, HDL-C level, triglycerides, smoking, statin use, kV.

Model 2 − necrotic core (East Asian ethnicity, age, and hypercholesteremia); fibrofatty plaque (East Asian ethnicity, BMI, hypertension, smoking, triglycerides level); fibrous plaque (East Asian ethnicity, BMI, hypertension, smoking, triglycerides level); calcified plaque (East Asian ethnicity, total cholesterol level, LDL-C level).

Regression for other variables in multivariate analysis not shown. *Model 1*: Only triglycerides demonstrated an association with increasing fibrofatty plaque (ß = 7.9; 95% CI 0.26 to 15.57; p = 0.043) and decreasing fibrous plaque composition (ß = −9.9; 95% CI −19.5 to −0.35; p = 0.042). *Model 2:* East Asian ethnicity was the only independent variable associated with all outcomes of interest.

95% CI − 95% confidence Intervals.

Bold p values represent <0.05.

fibrofatty plaque and a higher composition of fibrous plaque compared with Caucasians may provide a mechanistic basis for some of the observed differences in cardiovascular mortality and incidence of ACS between ethnic groups. Earlier studies have reported an independently lower prevalence and quantity of coronary calcification in East Asians compared with Caucasians.[16,17] In our cohort, there was a trend toward lower calcified plaque burden and composition in East Asians, although this did not reach significance.

Ethnic differences in coronary atherosclerosis have predominately been reported in South Asian populations compared with Caucasians as a means to investigate the over representation of South Asians with cardiovascular disease burden, severity, and associated mortality.[18] Several studies with matched cohorts have reported South Asian ethnicity as independently associated with higher plaque volumes and composition with noncalcified plaque.[19,20] The contrasting clinical outcomes and plaque characteristics between South Asians and East Asians further emphasize the need for separate subgroup classification of Asian populations in clinical trials and population-based registries.

Underlying mechanisms for the differences in plaque composition between East Asians and Caucasians are unclear. The contrasting cardiovascular outcomes between ethnic groups can only be partially explained by conventional risk factors, suggesting the need to consider the role of genetic or environmental factors such as diet, exercise, and medication compliance as potentially contributing to differences in plaque morphology.[21,22] Lipoprotein(a) [Lp (a)] has been identified as a strong and highly heritable risk factor for CAD with levels determined by variations in the LPA gene differing substantially within ethnic groups.[23,24] Human and animal studies suggest its potential role in formation of necrotic core and plaques vulnerable to rupture.[25] The serum concentration of Lp(a) is predominately determined by variations in the LPA gene locus.[26] Ethnic differences in the LPA gene and Lp(a) levels have been described with the highest levels observed in Africans,

followed by South Asians, Caucasians, and the lowest in East Asians.[25,27] Despite these differences, Lp(a) remains an independent cardiovascular risk factor across all ethnic groups, including East Asians.[25,28] Therefore, ethnic variations in the LPA gene may potentially influence plaque burden and composition to explain differences in cardiovascular outcomes.

There are a number of limitations in this study. First, this is a small cross-sectional study in whom potential confounders such as ethnic differences in diet, levels of physical activity, duration of cardiovascular risk factor exposure or duration of treatment, medication compliance, inflammatory biomarkers, and levels of Lp(a) have not been accounted for in the analysis. Second, as thresholds for noncalcified plaque components on CTA have been defined from intravascular ultrasound (IVUS) studies, significant overlap exists between the densities of fibrous and lipid-rich plaques.[6] Therefore, CT-derived categories of plaque composition likely represent gradations of risk in plaque rather than distinct differences in histopathology.[29] Furthermore, the prognostic implications of isolated differences in plaque composition in the absence of differences in plaque burden are unknown. Third, we observed no significant difference in plaque volume and burden between the ethnic groups. This may reflect the study's small sample size in a stable cohort of patients. Larger adequately powered studies are required to confirm these observations. Fourth, different scan parameters according to differences in BMI were used which may potentially influence plaque attenuation and characterization[30]; however, no association with tube voltage and quantitative plaque composition was demonstrated on multivariate analysis or in the propensity matched cohort. Lastly, the generalizability of these results may be limited as the cohort was taken from a single center in Australia. Potential differences between migrant and native East Asian populations and regional differences between ethnic groups remain unaccounted.

Conclusion

Based on this matched cohort with comparable overall plaque volume and burden, East Asians demonstrated significantly less composition of highest risk noncalcified plaque (necrotic core and fibrofatty plaque) and a higher composition of low-risk fibrous plaque compared with Caucasians.

Disclosures

Dr. Ihdayhid has received advisory board honoraria from Boston Scientific. Associate Professor Ko has received honorarium and speaker fees from Medtronic, St Jude, Novartis, Pfizer, Bristol-Myers Squibb, and Lilly. Professor Achenbach has received research grants from Siemens Healthcare and Bayer.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.06.020.

1. Bansal N, Fischbacher CM, Bhopal RS, Brown H, Steiner MF, Capewell S, Scottish H, Ethnicity Linkage S. Myocardial infarction incidence and survival by ethnic group: Scottish Health and Ethnicity Linkage retrospective cohort study. *BMJ Open* 2013;3:e003415.
2. Van Oeffelen AAM, Vaartjes I, Stronks K, Bots ML, Agyemang C. Incidence of acute myocardial infarction in first and second generation minority groups: Does the second generation converge towards the majority population? *Int J Cardiol* 2013;168:5422–5429.
3. Mak KH, Chia KS, Kark JD, Chua T, Tan C, Foong BH, Lim YL, Chew SK. Ethnic differences in acute myocardial infarction in Singapore. *Eur Heart J* 2003;24:151–160.
4. Jose PO, Frank ATH, Kapphahn KI, Goldstein BA, Eggleston K, Hastings KG, Cullen MR, Palaniappan LP. Cardiovascular disease mortality in Asian Americans. *J Am Coll Cardiol* 2014;64:2486–2494.
5. Narula J, Strauss HW. The popcorn plaques. *Nat Med* 2007;13:532–534.
6. Voros S, Rinehart S, Qian Z, Vazquez G, Anderson H, Murrieta L, Wilmer C, Carlson H, Taylor K, Ballard W, Karmpaliotis D, Kalynych A, Brown C 3rd. Prospective validation of standardized, 3-dimensional, quantitative coronary computed tomographic plaque measurements using radiofrequency backscatter intravascular ultrasound as reference standard in intermediate coronary arterial lesions: results from the ATLANTA (assessment of tissue characteristics, lesion morphology, and hemodynamics by angiography with fractional flow reserve, intravascular ultrasound and virtual histology, and noninvasive computed tomography in atherosclerotic plaques) I study. *JACC Cardiovasc Interv* 2011;4:198–208.
7. Chang HJ, Lin FY, Lee SE, Andreini D, Bax J, Cademartiri F, Chinnaiyan K, Chow BJW, Conte E, Cury RC, Feuchtner G, Hadamitzky M, Kim YJ, Leipsic J, Maffei E, Marques H, Plank F, Pontone G, Raff GL, van Rosendael AR, Villines TC, Weirich HG, Al'Aref SJ, Baskaran L, Cho I, Danad I, Han D, Heo R, Lee JH, Rivzi A, Stuijfzand WJ, Gransar H, Lu Y, Sung JM, Park HB, Berman DS, Budoff MJ, Samady H, Shaw LJ, Stone PH, Virmani R, Narula J, Min JK. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol* 2018;71:2511–2522.
8. Shah BR, Chiu M, Amin S, Ramani M, Sadry S, Tu JV. Surname lists to identify South Asian and Chinese ethnicity from secondary data in Ontario, Canada: a validation study. *BMC Med Res Methodol* 2010;10:42.
9. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2014;8:342–358.
10. Gaur S, Ovrehus KA, Dey D, Leipsic J, Botker HE, Jensen JM, Narula J, Ahmadi A, Achenbach S, Ko BS, Christiansen EH, Kaltoft AK, Berman DS, Bezerra H, Lassen JF, Norgaard BL. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. *Eur Heart J* 2016;37:1220–1227.
11. Dey D, Schepis T, Marwan M, Slomka PJ, Berman DS, Achenbach S. Automated three-dimensional quantification of noncalcified coronary plaque from coronary CT angiography: comparison with intravascular US. *Radiology* 2010;257:516–522.
12. de Graaf MA, Broersen A, Kitslaar PH, Roos CJ, Dijkstra J, Lelieveldt BP, Jukema JW, Schalij MJ, Delgado V, Bax JJ, Reiber JH, Scholte AJ. Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. *Int J Cardiovasc Imaging* 2013;29:1177–1190.
13. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med* 2008;3:17.
14. Versteylen MO, Kietselaer BL, Dagnelie PC, Joosen IA, Dedic A, Raaijmakers RH, Wildberger JE, Nieman K, Crijns HJ, Niessen WJ, Daemen MJ, Hofstra L. Additive value of semiautomated quantification of coronary artery disease using cardiac computed tomographic angiography to predict future acute coronary syndrome. *J Am Coll Cardiol* 2013;61:2296–2305.
15. Hell MM, Motwani M, Otaki Y, Cadet S, Gransar H, Miranda-Peats R, Valk J, Slomka PJ, Cheng VY, Rozanski A, Tamarappoo BK, Hayes S, Achenbach S, Berman DS, Dey D. Quantitative global plaque characteristics from coronary computed tomography angiography for the prediction of future cardiac mortality during long-term follow-up. *Eur Heart J Cardiovasc Imaging* 2017;18:1331–1339.

16. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2005;111:1313–1320.
17. Budoff MJ, Nasir K, Mao S, Tseng PH, Chau A, Liu ST, Flores F, Blumenthal RS. Ethnic differences of the presence and severity of coronary atherosclerosis. *Atherosclerosis* 2006;187:343–350.
18. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, Kelemen L, Yi C, Lonn E, Gerstein H, Hegele RA, McQueen M. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet* 2000;356: 279–284.
19. Villadsen PR, Petersen SE, Dey D, Zou L, Patel S, Naderi H, Gruszczynska K, Baron J, Davies LC, Wragg A, Botker HE, Pugliese F. Coronary atherosclerotic plaque burden and composition by CT angiography in Caucasian and South Asian patients with stable chest pain. *Eur Heart J Cardiovasc Imaging* 2017;18:556–567.
20. Adams DB, Narayan O, Munnur RK, Cameron JD, Wong DT, Talman AH, Harper RW, Seneviratne SK, Meredith IT, Ko BS. Ethnic differences in coronary plaque and epicardial fat volume quantified using computed tomography. *Int J Cardiovasc Imaging* 2017;33:241–249.
21. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. *Diabetes Care* 2013;36:1789–1796.
22. Wu Y, Benjamin EJ, MacMahon S. Prevention and control of cardiovascular disease in the rapidly changing economy of China. *Circulation* 2016;133:2545–2560.
23. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M, Consortium P. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361:2518–2528.
24. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301:2331–2339.
25. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol* 2017;69: 692–711.
26. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. *J Clin Investig* 1992;90:52–60.
27. Lee SR, Prasad A, Choi YS, Xing C, Clopton P, Witztum JL, Tsimikas S. LPA gene, ethnicity, and cardiovascular events. *Circulation* 2017;135:251–263.
28. Dai W, Long J, Cheng Y, Chen Y, Zhao S. Elevated plasma lipoprotein(a) levels were associated with increased risk of cardiovascular events in Chinese patients with stable coronary artery disease. *Sci Rep* 2018;8:7726.
29. Lee SE, Chang HJ, Sung JM, Park HB, Heo R, Rizvi A, Lin FY, Kumar A, Hadamitzky M, Kim YJ, Conte E, Andreini D, Pontone G, Budoff MJ, Gottlieb I, Lee BK, Chun EJ, Cademartiri F, Maffei E, Marques H, Leipsic JA, Shin S, Choi JH, Chinnaiyan K, Raff G, Virmani R, Samady H, Stone PH, Berman DS, Narula J, Shaw LJ, Bax JJ, Min JK. Effects of statins on coronary atherosclerotic plaques: the PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) study. *JACC Cardiovasc Imaging* 2018;135:251–261.
30. Dalager MG, Bottcher M, Dalager S, Andersen G, Thygesen J, Pedersen EM, Botker HE. Imaging atherosclerotic plaques by cardiac computed tomography in vitro: impact of contrast type and acquisition protocol. *Investig Radiol* 2011;46:790–795.