Arteriosclerosis, Thrombosis, and Vascular Biology

ORIGINAL RESEARCH

Lipid-Related Polygenic Risk Score and Its Association With Plaque Rupture Versus Erosion

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BACKGROUND: Distinct plaque morphologies underlie the major causes of acute coronary syndrome and sudden cardiac death. We used polygenic risk scores (PRSs) for hypercholesterolemia and hypertriglyceridemia, 2 major risk factors for coronary artery disease (CAD), to evaluate the relative contributions of these risk factors to specific plaque morphologies, specifically plaque rupture and erosion.

METHODS: DNA was extracted from formalin-fixed paraffin-embedded tissues and genotyped for 954 subjects from our sudden death autopsy registry, with cause of death determined by autopsy. LDL (low-density lipoprotein)–specific and triglyceride-specific PRSs were constructed based on the Global Lipids Genetics Consortium genome-wide association study results, excluding variants associated with both traits ($P<0.05$).

RESULTS: Subjects in the highest LDL-specific PRS quintile had significantly more plaque rupture, ≥75% lumen narrowing, thrombotic CAD, and CAD-related death compared with those in the lowest quintile. After adjusting for the first 10 principle components, LDL-specific PRS remained significantly associated with rupture (odds ratio [OR], 1.22 per SD [95% CI, 1.04–1.43]; $P=0.017$), ≥75% lumen narrowing (OR, 1.33 [95% CI, 1.13–1.57]; $P<0.001$), thrombotic CAD (OR, 1.21 [95% CI, 1.04–1.41]; $P=0.016$), and CAD-related death (OR, 1.31 [95% CI, 1.13–1.52]; $P<0.001$). In contrast, triglyceride-specific PRS was significantly associated with thrombotic CAD (OR, 1.20 [95% CI, 1.03–1.40]; $P=0.020$) and showed a trend toward association with plaque rupture (OR, 1.15 [95% CI, 0.98–1.35]; $P=0.091$). No association was observed between LDL-/triglyceride-specific PRS and plaque erosion.

CONCLUSIONS: This is the first study to associate lipid PRSs with specific plaque morphologies, revealing distinct pathogenic mechanisms underlying plaque rupture and erosion. Early genetic risk stratification and subsequent lipid-lowering interventions may provide substantial clinical benefits in mitigating cardiovascular risk, particularly in relation to plaque rupture. Our findings raise questions about the effectiveness of such strategies in preventing plaque erosion, suggesting the need for further investigation into its underlying pathogenesis.

Key Words: acute coronary syndrome ■ atherosclerosis ■ coronary artery disease ■ death, sudden, cardiac ■ risk factors

Sudden cardiac death caused by coronary artery disease (CAD) is a leading cause of mortality worldwide.[1] Dyslipidemia is recognized as one of the most prevalent and modifiable risk factors for CAD.[2,3] Lipid-lowering therapies, such as statins and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, have demonstrated significant efficacy in mitigating cardiovascular risk, reducing major vascular events by ≈21% per 1.0-mmol/L reduction in LDL-C (low-density lipoprotein cholesterol) levels.[4] However, despite these advancements, a substantial residual risk persists, highlighting the ongoing challenges in preventing acute coronary syndromes (ACSs) and sudden cardiac death.

Levels of LDL-C and triglycerides have a strong genetic basis, with a heritability of 40% to 60%.[5,6] These heritabilities have primarily a polygenic basis, as multiple

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Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
AD	allele dosage
CAD	coronary artery disease
FFPE	formalin-fixed paraffin-embedded
GWAS	genome-wide association study
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
OR	odds ratio
PC	principal component
PCSK9	proprotein convertase subtilisin/kexin type 9
PRS	polygenic risk score
QC	quality control
SNP	single-nucleotide polymorphism

common variants cumulatively influence LDL-C and triglyceride levels.[7,8] Polygenic risk scores (PRSs), which aggregate the weighted sum of risk variants across multiple loci, have been used to quantify an individual's polygenic risk for various diseases.[9] We previously reported that a CAD-related PRS is strongly associated with advanced atherosclerotic features at the histopathologic level.[10] However, current strategies for primary prevention are limited to addressing CAD risk factors, mainly through lipid-lowering therapies and lifestyle modification.

CAD-related pathologies are diverse. The major pathological mechanisms of thrombotic sudden coronary death are plaque rupture (60%), plaque erosion (35%), and calcified nodule (5%). While clinical studies have clearly demonstrated the benefit of lowering LDL (low-density lipoprotein) and, to some extent, triglyceride in reducing the risk of ACS and cardiovascular mortality, it remains unknown how effective these strategies are in preventing the 2 major causes of ACS (ie, plaque rupture and plaque erosion), as clinical studies do not differentiate the pathological causes of ACS. Furthermore, although previous studies have shown that single-nucleotide polymorphisms (SNPs) exclusively affecting LDL-C or triglyceride levels are associated with CAD risk,[11] direct mechanistic links between these genetic variants and specific forms of atherosclerosis have never been studied.

Plaque rupture typically occurs due to the disruption of a thin fibrous cap with subsequent exposure of a necrotic, lipid-rich core to circulating blood. In contrast, plaque erosion is less lipid-rich and is characterized by endothelial denudation overlying an intact fibrous cap, which distinguishes it from rupture or rupture-prone plaques. Although lowering LDL-C and triglycerides reduces CAD-related events, it does not fully eliminate them. Thus, whether and how specific lipid-related PRSs associate with plaque ruptures and plaque erosions remains an important and unresolved public health question.[12,13] In this context, assessing lipid-related PRSs and their relationship with histopathologic features is crucial, as such analyses may also underscore the need to explore nonlipid factors that play critical roles in the pathogenesis of each type of plaque. In this study, we hypothesized that polygenic risk for LDL-C and triglycerides would demonstrate a stronger association with plaque rupture than with plaque erosion, reflecting distinct genetic contributions to the underlying pathobiology of ACS.

What Are the Clinical Implications?

Sudden cardiac death due to coronary artery disease (CAD) remains a major global health burden and is largely driven by 2 distinct plaque morphologies: plaque rupture and plaque erosion. Dyslipidemia is the most common and modifiable CAD risk factor, yet clinical trials evaluating LDL-C (low-density lipoprotein cholesterol) and triglyceride lowering rarely distinguish the pathological mechanisms underlying CAD events. Although many lipid-associated genetic variants have been linked to CAD, their relevance to specific plaque phenotypes has remained unclear. To address this gap, we analyzed a unique autopsy registry of 954 individuals who died from sudden death and evaluated whether polygenic risk scores (PRSs) for LDL-C and triglyceride were differentially associated with plaque morphology. A higher LDL PRS was significantly associated with plaque rupture, >75% luminal narrowing, thrombotic CAD, and CAD-related death. Similarly, higher triglyceride-PRS was significantly associated with thrombotic CAD and showed a trend toward rupture. In contrast, neither PRS was linked to plaque erosion. This study is the first to directly associate lipid-related PRSs with histopathologically defined CAD phenotypes. Integrating genomic risk with detailed pathology provides a new insight into the biological drivers of rupture versus erosion and may help refine risk stratification for rupture-mediated events.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Population

The study population has been previously described.[10] Briefly, between 1994 and 2015, CVPath Institute, Inc, received 4327 hearts from the Maryland Office of the Chief Medical Examiner, belonging to individuals aged ≥18 years who died of unexpected sudden death. Unexpected sudden death is defined as a witnessed sudden death occurring within 6 hours of symptom

onset from a stable medical condition or the death of an individual who was seen in stable condition within 24 hours before death, as previously described.[14,15] Information on cardiovascular risk factors and comorbidities was obtained from the subjects' medical history as documented in the medical examiner's report. Self-reported ancestry was identified from the Office of the Chief Medical Examiner report through inquiry of family members.

To examine ancestry-based differences, only subjects self-identified as having European or African American ancestry were selected for genotyping; those of other ancestries were excluded due to insufficient sample sizes for reliable analysis. From the entire cohort, 2455 individuals were randomly selected for genotyping, including 1490 self-reported European ancestry subjects (Erasmus data set) and 965 self-reported African American ancestry subjects, which comprised 2 data sets based on differences in genotyping batch (SCA1 and SCA2). Of these, 1238 subjects were excluded due to insufficient DNA sample quality, and an additional 263 subjects were excluded due to missing or inconsistent data or a history of heart transplantation. Ultimately, 954 cases were included in the final analysis, comprising 392 cases from European ancestry and 562 cases from African ancestry groups (Figure S1). The protocol for this study was approved by the institutional review board of CVPath Institute, Inc, and a waiver of consent was granted due to the use of autopsy-related materials as the primary source.

DNA Extraction and Genotyping

Genomic DNA was isolated from formalin-fixed paraffin-embedded (FFPE) tissue using the QIAamp DNA FFPE Tissue Kit (Qiagen), following the manufacturer's protocol. DNA quality was assessed using the TapeStation system (Agilent), and only samples that met the quality criteria for the DNA Restoration Kit and Infinium FFPE (Illumina) were selected for library preparation. Genotyping and imputation were performed in 2 separate batches at different locations, as previously documented.[10] The first data set, the European ancestry cohort, included 1490 samples from individuals who self-identified as having European ancestry. Genotyping for this cohort was conducted at the Human Genomics Facility Genetic Laboratory at Erasmus University in Rotterdam, the Netherlands. The second data set, the African American ancestry cohort, consisted of 965 samples from individuals who self-identified as having African American ancestry, with genotyping performed at the UTHealth Human Genetics Center Laboratory at The University of Texas.

European Ancestry Cohort

Genotyping was performed on 1490 samples using the Illumina Global Screening Array, covering 576 876 SNPs. Quality control (QC) was conducted with PLINK, version 1.07.[16] Before imputation, SNP-level QC was applied based on call rate (<90%), minor allele frequency (<0.05), and Hardy-Weinberg equilibrium ($P<1\times10^{-8}$), resulting in a total of 484 979 SNPs retained for analysis. For sample-level QC, 235 samples were excluded due to extremely low call rates (<90%), and 1 sample was removed for heterozygosity deviations or F-statistic abnormalities. Imputation was then carried out using the Michigan Imputation Server with the Haplotype Reference Consortium reference panel (hg19/GRCh37). Postimputation QC included heterozygosity assessments, sample call rate evaluation, kinship analysis, and principal component (PC) analysis. This process led to the removal of an additional 628 samples, including 327 duplicate samples, 136 highly related individuals (identified using a kinship coefficient >0.1875, indicative of relationships between second- and third-degree relatives), 90 samples with low call rates (<95%), 53 samples with sex mismatches in PLINK, and 22 samples exhibiting excessive heterozygosity (F≤mean −1.9×SD). Ancestry groups were determined through PC analysis using the 1000 Genomes reference data set,[17] and 3 genomic outliers were subsequently removed. After comprehensive QC, 623 samples remained. Following exclusion of cases with insufficient clinical or autopsy data or with a history of heart transplantation, 392 cases remained for PRS calculation.

African American Ancestry Cohort

The African American ancestry cohort was compiled by the SCD Working Group of the CHARGE Consortium for the purpose of harmonizing genotypes to be used for a genome-wide association prior analysis of sudden cardiac arrest risk.[18] For logistical reasons, genotyping for the African American ancestry cohort was performed across 4 different platforms: the Illumina MEGAv2 (Ex) Consortium Chip, the Illumina Exome Chip, the Illumina HumanOmniExpress-24 Chip, and the Illumina African Diaspora Power Chip. We initially selected 588 samples genotyped using the Illumina MEGAv2 (Ex) Consortium Chip (SCA1) and 377 samples genotyped on ≥1 of the other 3 platforms (SCA2). Of the SCA2 samples, 150 samples genotyped on only 1 of the 3 platforms were finally excluded. Array-specific QC was performed using PLINK, versions 1.07 and 1.90,[16] to remove samples with a call rate <95% (n=154) and samples failing other QC metrics such as sex mismatch, duplicates, potential contamination, excessive heterozygosity, or high relatedness (n=39). Following array-specific QC, 622 samples remained. Genotypes for these samples were then imputed separately by array on the Michigan Imputation Server,[19] using the Trans-Omics for Precision Medicine Freeze 5 (hg38) reference panel. This process included lift over from hg19 to hg38, as well as phasing (using Eagle). Imputed genotypes were then merged across arrays, and a second round of postimputation QC was performed, which resulted in the exclusion of an additional 28 samples, including 19 for excessive heterozygosity and 9 for relatedness across arrays. After further exclusion of cases with insufficient clinical or autopsy information or with a heart transplantation history, the final data set consisted of 562 samples (Figure S1).

PRS Construction

We constructed 2 types of lipid-associated PRS: LDL-specific PRS and triglyceride-specific PRS. These scores were calculated based on previously published trans-ancestry summary genome-wide association study (GWAS) results from the Global Lipids Genetics Consortium,[7] which performed a comprehensive multiancestry meta-analysis of lipid levels in ≈1.65 million individuals, including ≈15 million SNPs. PRSice, version 2.3.5, was used for PRS calculations. We identified all SNPs that met genome-wide significance ($P<5.0\times10^{-8}$) for LDL-C and triglyceride. Within each trait, SNPs were pruned and clumped

using a physical distance threshold of 250 kb and a linkage disequilibrium r^2 threshold of 0.05. To identify SNPs that were specific for each trait, we excluded SNPs in LDL-C, which were associated with triglyceride at $P<0.05$ and similarly removed SNPs in triglyceride, which were associated with LDL-C at $P<0.05$. This resulted in 2536 LDL-specific SNPs and 2533 triglyceride-specific SNPs in the European ancestry cohort, as well as 3313 LDL-specific SNPs and 3112 triglyceride-specific SNPs in the African American cohort, for PRS construction. For each SNP, allele dosage (AD) was calculated as

$$AD = 2 \times (AA) + 1 \times (AB) + 0 \times (BB)$$

where AA, AB, and BB represent the homozygous, heterozygous, and nonrisk genotypes, respectively. The PRS for each individual was then calculated as

$$PRS = \sum (\beta \times AD)$$

where β is the effect size for each SNP. Subjects within each cohort were divided into 5 PRS quintiles as described previously.[10]

Histopathologic Analysis

All cases underwent comprehensive cardiac examination by expert cardiovascular pathologists, as previously described.[14,15] Coronary arteries were perfusion-fixed with formalin at a pressure of 100 mm Hg, decalcified if necessary, and sectioned into 3-mm slices for histological examination. Tissue sections were processed through dehydration, clearing, paraffin embedding, and sectioning into 4-μm slices, followed by staining with hematoxylin and eosin and Movat pentachrome. The right and left ventricles were sectioned at 1-cm intervals from the apex to the base, with each slice measuring 1.5 to 2.0 cm in length. These sections were inspected for signs of myocardial infarction. In hearts without evidence of myocardial infarction, at least 1 section from each ventricular wall underwent histological preparation. In cases with myocardial infarction, additional sections from the infarcted regions were also prepared.

Plaque morphologies, including plaque rupture, plaque erosion, other thrombosis (ie, calcified nodules and stent thrombosis), calcification, thin-cap fibroatheroma, and intraplaque hemorrhage, were systematically evaluated for all subjects. Plaque rupture is defined by the disruption of the fibrous cap, where the luminal thrombus is in continuity with the underlying necrotic core.[20] Plaque erosion is defined as the presence of an acute luminal thrombus in direct contact with the intima in an area lacking endothelial cells, with a thick fibrous cap and no disruption.[20] Calcified nodule is identified by fibrous cap disruption caused by eruptive calcific nodules, accompanied by either an occlusive or nonocclusive platelet/fibrin thrombus.[20] Stent thrombosis is defined as the presence of an acute occlusive or nonocclusive mural thrombus within a coronary artery stent.[21] Thin-cap fibroatheroma is defined as a large necrotic core covered by a thin (<65 μm) fibrous cap heavily infiltrated by macrophages.[22] Intraplaque hemorrhage is defined as a lesion containing red blood cells and fibrin with a necrotic core.[20]

Morphometric analysis of the external elastic lamina, internal elastic lamina, lumen, necrotic core area, and percent stenosis, calculated as 100×([internal elastic lamina area−lumen area]/internal elastic lamina area), was performed for each vessel from each subject (ZEN, version 2.3; Carl Zeiss, Germany). The maximum percent stenosis was used to conduct a semiquantitative analysis of atherosclerosis severity, categorized as follows: <25% maximum stenosis was defined as no atherosclerosis, 25% to 49% as mild atherosclerosis, 50% to 74% as moderate atherosclerosis, and ≥75% as severe atherosclerosis.

Thrombotic CAD was defined as the presence of plaque rupture, plaque erosion, and other thrombosis. CAD-associated death was defined as having at least 1 epicardial coronary artery narrowed by ≥75% in cross-sectional area due to an atherosclerotic plaque or the presence of coronary thrombosis. The relationship between each phenotype is illustrated in Figure S2.

Statistical Analysis

The PC analysis integrating 1000 Genomes reference populations[17] confirmed ancestral similarity between pooled European samples and our European ancestry cohort, and between pooled African ancestry samples and our African American ancestry cohort (SCA1 and SCA2)[18] (Figure S3). Based on these results, the 2 African American ancestry cohorts were merged for subsequent analysis.

Continuous variables were presented as mean±SD, and categorical variables were presented as numbers and percentages. Comparisons between 2 groups were performed using the Student t test for normally distributed data, the Mann-Whitney U test for nonnormally distributed data, and the χ^2 test for categorical variables. Categorical variables were adjusted with covariates using logistic regression analysis, and continuous variables were adjusted using ANCOVA.

Each data set was analyzed separately, adjusting for age, sex, body mass index, and 10 ancestry-specific PCs, with PRS independently standardized using Z scores. In addition, the overall cohort was then analyzed, adjusted for age, sex, body mass index, self-reported ancestry, and 10 PCs calculated for the entire cohort. Logistic regression analyses were conducted to assess the odds of binary outcomes (eg, plaque rupture) per SD increase in standardized PRS (Z score) and across PRS quintiles using the first quintile as the reference. For the across-ancestry meta-analysis, we standardized the estimates by dividing the weighted estimates by their standard errors. The inverse of the variances, calculated as the square of the standard errors, were used as weights. Statistical analyses were performed using GMP, version 18.

RESULTS

Clinical and Histopathologic Characteristics

Baseline characteristics of 562 subjects of self-reported African ancestry and 392 subjects of self-reported European ancestry with available genomic data are summarized in Table 1 and Table S1. The mean age was 48.8±14.7 years, and 75.7% were male. Subjects in the European ancestry cohort were significantly older (53.2±15.1 versus 45.8±13.6 years; $P<0.001$) and had a higher proportion of males than the African American ancestry cohort (82.4% versus 71.0%; $P<0.001$). Regarding histopathologic findings, subjects in the European ancestry cohort exhibited significantly more advanced atherosclerotic plaque features, including plaque rupture, severe atherosclerosis (≥75% cross-sectional stenosis), larger maximum percent stenosis, higher prevalence of calcification,

Table 1. Baseline Clinical and Histopathologic Characteristics

	Overall cohort (n=954)	European ancestry cohort (n=392)	African American ancestry cohort (n=562)	*P* value
Clinical characteristics				
Age, y	48.8±14.7	53.2±15.1	45.8±13.6	<0.001
Male, n (%)	722 (75.7%)	323 (82.4%)	399 (71.0%)	<0.001
BMI, kg/m^2	30.1±7.4	29.3±6.4	30.6±8.0	0.16*
Hypertension, n (%)	555 (58.2%)	217 (55.4%)	338 (60.1%)	0.001*
Dyslipidemia, n (%)	127 (13.3%)	47 (12.0%)	80 (14.2%)	0.02*
Diabetes, n (%)	148 (15.5%)	49 (12.5%)	99 (17.6%)	0.005*
Smoking, n (%)	154 (16.1%)	99 (25.3%)	55 (9.8%)	<0.001*
Kidney disease, n (%)	65 (6.8%)	18 (4.6%)	47 (8.4%)	<0.001*
Histopathologic findings				
Thrombotic CAD, n (%)	426 (44.7%)	258 (65.8%)	168 (29.9%)	<0.001*
Rupture, n (%)	309 (32.4%)	201 (51.3%)	108 (19.2%)	<0.001*
Erosion, n (%)	95 (10.0%)	43 (11.0%)	52 (9.3%)	0.08*
Other coronary thrombosis, n (%)	22 (2.3%)	14 (3.6%)	8 (1.4%)	0.27*
Any coronary atherosclerosis, n (%)	762 (79.9%)	360 (91.8%)	402 (71.5%)	<0.001*
Severe atherosclerosis (≥75% cross-sectional stenosis), n (%)	591 (61.9%)	313 (79.8%)	278 (49.5%)	<0.001*
Maximum % stenosis	65.3±36.8	73.3±29.2	50.3±37.2	<0.001*
Calcification, n (%)	465 (48.7%)	116 (29.6%)	349 (62.1%)	<0.001*
Intraplaque hemorrhage, n (%)	150 (15.7%)	82 (20.9%)	68 (12.1%)	0.02*
TCFA, n (%)	149 (15.6%)	99 (25.3%)	50 (8.9%)	<0.001*
Cause of death (as filed by the medical examiner)				
CAD-associated	493 (51.7%)	250 (63.8%)	243 (43.2%)	<0.001*

BMI indicates body mass index; CAD, coronary artery disease; and TCFA, thin-cap fibroatheroma.

*Adjusted for age and sex. Continuous data are presented as mean±SD. Categorical data are presented as numbers and percentages. The Student *t* test and the χ^2 test were used for unadjusted analysis. Categorical variables were adjusted using logistic regression analysis, and continuous variables were adjusted using ANCOVA.

intraplaque hemorrhage, thin-cap fibroatheroma, thrombotic CAD, and CAD-associated death. Importantly, plaque rupture, severe atherosclerosis, thrombotic CAD, and CAD-associated death were significantly related to older age and male sex, while plaque erosion was significantly associated with younger age and showed no significant association with sex in the overall cohort (Table S2). No correlation between LDL-/triglyceride-specific PRS and age was observed (Figure S4).

After dividing subjects in each data set into quintiles according to PRS, there were no significant differences in age, sex, body mass index, and clinical characteristics between the lowest and highest LDL- and triglyceride-specific PRS quintiles in each data set or in the overall cohort (Tables 2 and 3).

Difference of Histopathologic Characteristics Between Lipid PRS Quintiles

The frequency of rupture was significantly higher among subjects in the highest LDL-specific PRS quintile compared with those in the lowest quintile in the overall cohort (39.5% versus 26.7%; $P_{adjusted}$=0.002) and in the European ancestry cohort (62.8% versus 43.6%; $P_{adjusted}$=0.016). In contrast, there was little difference in the frequency of erosion between the highest and lowest LDL-PRS quintiles in either data set or the overall cohort ($P_{adjusted}$>0.77 for both). In the overall cohort, the highest quintile was also significantly associated with a greater presence of thrombotic CAD (50.0% versus 37.2%; $P_{adjusted}$=0.005) and higher incidence of CAD-associated death (61.6% versus 43.5%; $P_{adjusted}$<0.001). Subjects in the highest quintile had greater maximum percent stenosis (71.2% versus 59.8%; $P_{adjusted}$<0.001), with more subjects having severe atherosclerosis (72.6% versus 57.1%; $P_{adjusted}$<0.001). In the European ancestry cohort, CAD-associated death was more prevalent in the highest versus the lowest quintile (74.4% versus 55.1%; $P_{adjusted}$=0.013), with a higher prevalence of thrombotic CAD (73.1% versus 53.8%; $P_{adjusted}$=0.015). Any coronary atherosclerosis was more frequent in the highest compared with the lowest quintile (94.9% versus 88.5%; $P_{adjusted}$=0.034), with a higher frequency of severe atherosclerosis (91.0% versus 75.6%; $P_{adjusted}$=0.004) and calcification (75.6% versus 62.8%;

Table 2. Comparison Between the Highest and Lowest LDL-Specific PRS Quintiles

	Overall cohort (n=954)			European ancestry cohort (n=392)			African American ancestry cohort (n=562)		
	First quintile (n=191)	Fifth quintile (n=190)	*P* value	First quintile (n=78)	Fifth quintile (n=78)	*P* valuee	First quintile (n=113)	Fifth quintile (n=112)	*P* value
Clinical characteristics									
Age, y	48.6±14.9	48.7±14.4	0.94	54.7±15.6	52.9±15.0	0.47	44.4±12.8	45.8±13.2	0.42
Male, n (%)	141 (73.8%)	141 (74.2%)	0.93	66 (84.6%)	65 (83.3%)	0.83	75 (66.4%)	76 (67.9%)	0.81
BMI, kg/m^2	30.8±8.6	30.4±7.7	0.64	28.5±5.2	29.5±7.7	0.34	32.4±10.0	31.1±7.6	0.25
Hypertension, n (%)	110 (57.6%)	109 (57.4%)	0.67*	43 (55.1%)	46 (59.0%)	0.42†	67 (59.3%)	63 (56.2%)	0.42†
Dyslipidemia, n (%)	24 (12.6%)	32 (16.8%)	0.20*	9 (11.5%)	13 (16.7%)	0.26†	15 (13.3%)	19 (17.0%)	0.55†
Diabetes, n (%)	31 (16.2%)	28 (14.7%)	0.76*	8 (10.3%)	7 (9.0%)	0.76†	23 (20.4%)	21 (18.8%)	0.73†
Smoking, n (%)	25 (13.1%)	31 (16.3%)	0.46*	18 (23.1%)	23 (29.5%)	0.64†	7 (6.2%)	8 (7.1%)	0.67†
Kidney disease, n (%)	14 (7.3%)	14 (7.4%)	0.98*	4 (5.1%)	4 (5.1%)	0.73†	10 (8.8%)	10 (8.9%)	0.64†
Histopathologic findings									
Thrombotic CAD, n (%)	71 (37.2%)	95 (50.0%)	0.005*	42 (53.8%)	57 (73.1%)	0.015†	29 (25.7%)	38 (33.9%)	0.29†
Rupture, n (%)	51 (26.7%)	75 (39.5%)	0.002*	34 (43.6%)	49 (62.8%)	0.016†	17 (15.0%)	26 (23.2%)	0.14†
Erosion, n (%)	18 (9.4%)	16 (8.4%)	0.80*	7 (9.0%)	6 (7.7%)	0.77†	11 (9.7%)	10 (8.9%)	0.78†
Other coronary thrombosis, n (%)	2 (1.3%)	4 (2.4%)	1.00*	1 (2.4%)	2 (3.5%)	0.13†	1 (0.9%)	2 (1.8%)	1.00†
Any coronary atherosclerosis, n (%)	144 (75.4%)	157 (82.6%)	0.067*	69 (88.5%)	74 (94.9%)	0.034†	75 (66.4%)	83 (74.1%)	0.26†
Severe atherosclerosis (≥75% cross-sectional stenosis), n (%)	109 (57.1%)	138 (72.6%)	<0.001*	59 (75.6%)	71 (91.0%)	0.004†	50 (44.2%)	67 (59.8%)	0.027†
Maximum % stenosis	59.8±38.3	71.2±35.8	<0.001*	74.2±32.5	85.2±23.4	0.002†	49.8±39.0	61.5±39.6	0.022†
Calcification, n (%)	91 (47.6%)	103 (54.2%)	0.19*	49 (62.8%)	59 (75.6%)	0.018†	42 (37.2%)	44 (39.3%)	0.48†
Intraplaque hemorrhage, n (%)	29 (15.2%)	37 (19.5%)	0.14*	18 (23.1%)	20 (25.6%)	0.62†	11 (9.7%)	17 (15.2%)	0.38†
TCFA, n (%)	31 (16.2%)	34 (17.9%)	0.65*	21 (26.9%)	25 (32.1%)	0.44†	10 (8.8%)	9 (8.0%)	0.82†
Cause of death (as filed by the medical examiner)									
CAD-associated	83 (43.5%)	117 (61.6%)	<0.001*	43 (55.1%)	58 (74.4%)	0.013†	40 (35.4%)	59 (52.7%)	0.010†

The Student *t* test and the χ^2 test were used for unadjusted analysis. Categorical variables were adjusted using logistic regression analysis, and continuous variables were adjusted using ANCOVA. BMI indicates body mass index; CAD, coronary artery disease; LDL, low-density lipoprotein; PRS, polygenic risk score; and TCFA, thin-cap fibroatheroma.

*Adjusted for age, sex, self-reported ancestry, and the first 10 principal components.

†Adjusted for age, sex, and the first 10 principal components.

$P_{adjusted}$=0.018), as well as greater maximum percent stenosis (85.2% versus 74.2%; $P_{adjusted}$=0.002) in the highest quintile. In the African American ancestry cohort, we observed a higher prevalence of CAD-associated death in the highest versus the lowest quintile (52.7% versus 35.4%; $P_{adjusted}$=0.010), and the presence of severe atherosclerosis was significantly greater in the highest quintile (59.8% versus 44.2%; $P_{adjusted}$=0.027) with greater maximum percent stenosis (61.5% versus 49.8%; $P_{adjusted}$=0.022; Figure 1; Table 2).

In contrast, comparison between the highest and lowest triglyceride-specific PRS quintiles in the overall cohort showed trends toward higher rates of rupture (39.3% versus 30.0%; $P_{adjusted}$=0.14), thrombotic CAD (53.9% versus 43.2%; $P_{adjusted}$=0.075), any coronary atherosclerosis (84.3% versus 76.8%; $P_{adjusted}$=0.095), and greater maximum percent stenosis (70.6% versus 61.7%; $P_{adjusted}$=0.062) in those within the highest quintile although these differences did not reach statistical significance (Figure 2; Table 3).

Logistic Regression Analysis Showing Association of Lipid PRS With Histopathology

Logistic regression analysis per SD increase in PRS, adjusted for age, sex, body mass index, and the first 10 PCs, demonstrated a significant association between LDL-specific PRS and increased odds of rupture (odds ratio [OR], 1.22 [95% CI, 1.04–1.43]; *P*=0.017), whereas no association was observed with erosion (OR, 1.03 [95% CI, 0.82–1.30]; *P*=0.80) in the overall cohort. In addition, LDL-specific PRS was significantly associated with higher odds of severe atherosclerosis (OR, 1.33 [95% CI, 1.13–1.57]; *P*<0.001), thrombotic CAD (OR, 1.21 [95% CI, 1.04–1.41]; *P*=0.016), and CAD-associated death (OR, 1.31 [95% CI, 1.13–1.52]; *P*<0.001) in the overall cohort

Table 3. Comparison Between the Highest and Lowest TG-Specific PRS Quintiles

	Overall cohort (n=954)			European ancestry cohort (n=392)			African American ancestry cohort (n=562)		
	First quintile (n=191)	Fifth quintile (n=191)	*P* value	First quintile (n=78)	Fifth quintile (n=79)	*P* value	First quintile (n=112)	Fifth quintile (n=112)	*P* value
Clinical characteristics									
Age, y	47.5±14.2	49.4±14.8	0.21	51.0±13.0	53.1±16.1	0.37	45.1±14.6	46.8±13.2	0.37
Male, n (%)	138 (72.6%)	149 (78.0%)	0.22	62 (79.5%)	69 (87.3%)	0.47	76 (67.9%)	80 (71.4%)	0.56
BMI, kg/m^2	30.1±6.9	29.9±6.7	0.71	30.2±6.7	29.1±5.6	0.29	30.4±7.5	30.1±7.1	0.76
Hypertension, n (%)	96 (50.5%)	112 (58.6%)	0.25*	35 (44.9%)	41 (51.9%)	0.85†	61 (54.5%)	71 (63.4%)	0.37†
Dyslipidemia, n (%)	24 (12.6%)	27 (14.1%)	0.83*	8 (10.3%)	10 (12.7%)	0.90†	16 (14.3%)	17 (15.2%)	0.81†
Diabetes, n (%)	27 (14.2%)	29 (15.2%)	0.97*	6 (7.7%)	8 (10.1%)	0.66†	21 (18.8%)	21 (18.8%)	0.77†
Smoking, n (%)	24 (12.6%)	31 (16.2%)	0.19*	14 (17.9%)	20 (25.3%)	0.19†	10 (8.9%)	11 (9.8%)	0.42†
Kidney disease, n (%)	16 (8.4%)	12 (6.3%)	0.19*	6 (7.7%)	3 (3.8%)	0.18†	10 (8.9%)	9 (8.0%)	0.71†
Histopathologic finding									
Thrombotic CAD, n (%)	82 (43.2%)	103 (53.9%)	0.075*	51 (65.4%)	56 (70.9%)	0.57†	31 (27.7%)	47 (42.0%)	0.056†
Rupture, n (%)	57 (30.0%)	75 (39.3%)	0.14*	36 (46.2%)	47 (59.5%)	0.15†	21 (18.8%)	28 (25.0%)	0.51†
Erosion, n (%)	19 (10.0%)	23 (12.0%)	0.49*	11 (14.1%)	7 (8.9%)	0.85†	8 (7.1%)	16 (14.3%)	0.062†
Other coronary thrombosis, n (%)	6 (3.7%)	5 (3.0%)	0.61*	4 (7.8%)	2 (3.6%)	0.11†	2 (1.8%)	3 (2.7%)	0.92†
Any coronary atherosclerosis, n (%)	146 (76.8%)	161 (84.3%)	0.095*	69 (88.5%)	73 (92.4%)	0.59†	77 (68.7%)	88 (78.6%)	0.13†
Severe atherosclerosis (≥75% cross-sectional stenosis), n (%)	113 (59.5%)	130 (68.1%)	0.19*	58 (74.4%)	66 (83.5%)	0.31†	55 (49.1%)	64 (57.1%)	0.40†
Maximum % stenosis	61.7±37.3	70.6±35.4	0.062*	74.0±30.6	82.0±28.3	0.37†	53.2±39.3	62.6±37.7	0.16†
Calcification, n (%)	89 (46.8%)	101 (52.9%)	0.40*	50 (64.1%)	56 (70.9%)	0.66†	39 (34.8%)	45 (40.2%)	0.61†
Intraplaque hemorrhage, n (%)	23 (12.1%)	29 (15.2%)	0.92*	12 (15.4%)	17 (21.5%)	0.36†	11 (9.8%)	12 (10.7%)	0.57†
TCFA, n (%)	30 (15.8%)	30 (15.7%)	0.43*	18 (23.1%)	19 (24.1%)	0.77†	12 (10.7%)	11 (9.8%)	0.58†
Cause of death (as filed by the medical examiner)									
CAD-associated	98 (51.6%)	110 (57.6%)	0.43*	50 (64.1%)	52 (65.8%)	0.97†	48 (42.9%)	58 (51.8%)	0.32†

The Student *t* test and the χ^2 test were used for unadjusted analysis. Categorical variables were adjusted using logistic regression analysis, and continuous variables were adjusted using ANCOVA. BMI indicates body mass index; CAD, coronary artery disease; PRS, polygenic risk score; TCFA, thin-cap fibroatheroma; and TG, triglyceride.

*Adjusted for age, sex, self-reported ancestry, and the first 10 principal components.

†Adjusted for age, sex, and the first 10 principal components.

(Table 4). In contrast, triglyceride-specific PRS was significantly associated with thrombotic CAD (OR, 1.20 [95% CI, 1.03–1.40]; *P*=0.020) and showed a trend toward an association with rupture (OR, 1.15 [95% CI, 0.98–1.35]; *P*=0.091) although it did not reach statistical significance. Similar to LDL-specific PRS, no association was observed between triglyceride-specific PRS and erosion (OR, 1.14 [95% CI, 0.91–1.44]; *P*=0.25; Table 5).

We subsequently conducted a logistic regression analysis, adjusting for age, sex, body mass index, and the first 10 PCs across all 5 quintiles. In the overall cohort, the odds of plaque rupture were twice as high in subjects in the highest LDL-specific PRS quintile compared with those in the lowest quintile (OR, 2.11 [95% CI, 1.30–3.43]), while no significant difference was found for erosion (OR, 0.92 [95% CI, 0.45–1.91]). Furthermore, the highest LDL-specific PRS quintile was associated with significantly increased odds of severe atherosclerosis (OR, 2.56 [95% CI, 1.53–4.26]), thrombotic CAD (OR, 1.92 [95% CI, 1.21–3.03]), and CAD-associated death (OR, 2.30 [95% CI, 1.48–3.56]; Table S3). Similarly, subjects in the highest triglyceride-specific PRS quintile exhibited significantly higher odds of thrombotic CAD (OR, 1.64 [95% CI, 1.04–2.58]) and a trend toward higher odds of rupture (OR, 1.52 [95% CI, 0.94–2.46]) compared with those in the lowest quintile though the latter did not reach statistical significance (Table S4).

Representative Cases Highlighting the Association Between Lipid PRS and Sudden Coronary Death

Figure 3 shows representative histological images of sudden death autopsy cases with high lipid PRS. Case 1 is a 69-year-old male of self-reported European ancestry with a history of coronary artery bypass grafting and percutaneous coronary intervention. Histological analysis reveals a large necrotic core (Figure 3A and 3B) and thrombotic

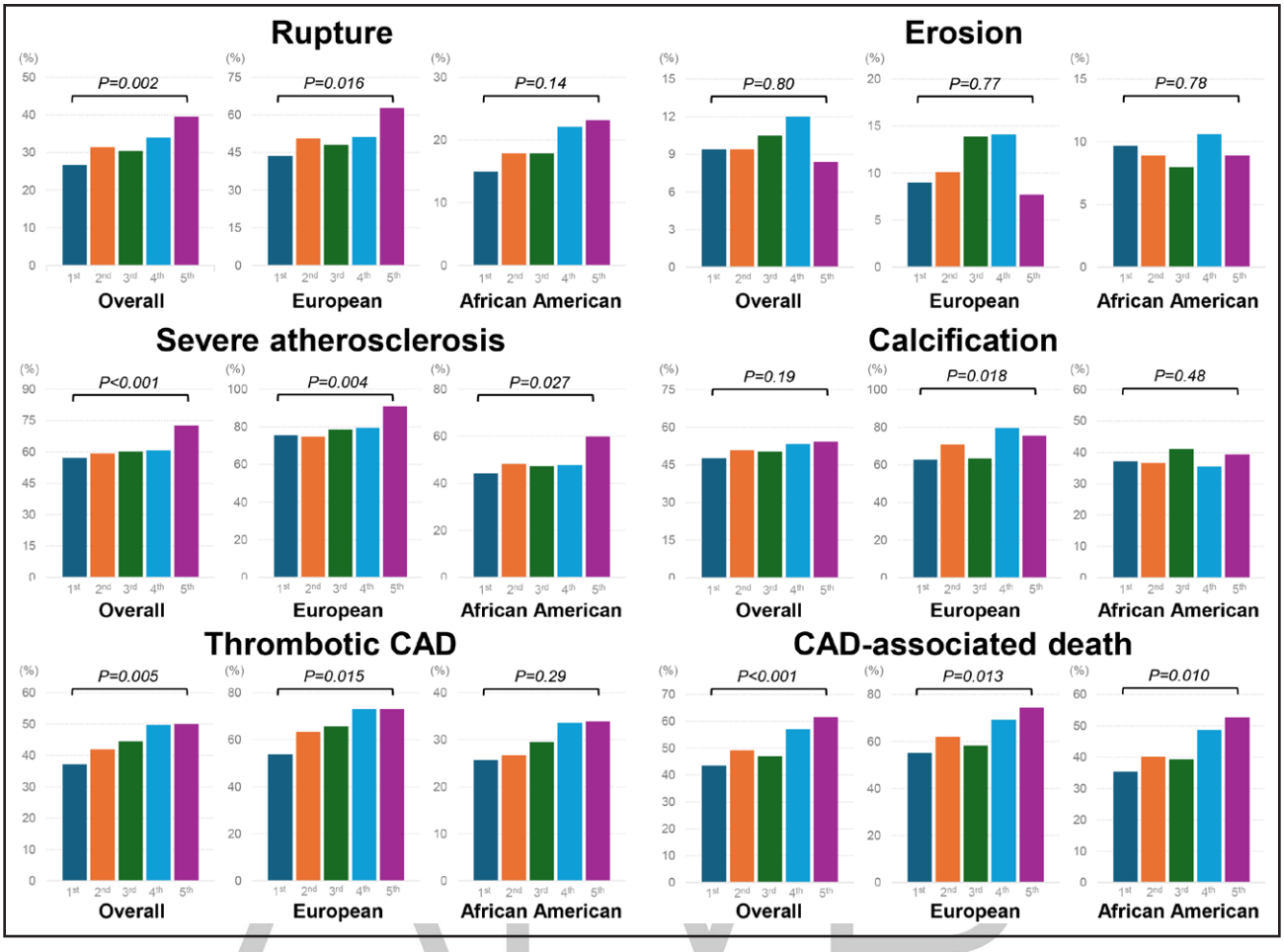

Figure 1. Association between LDL (low-density lipoprotein)–specific polygenic risk score (PRS) and histopathologic features. The vertical bars represent prevalence. Logistic regression analysis was used to compare the highest and lowest LDL-specific PRS quintiles. *P* values in the overall cohort are adjusted for age, sex, self-reported ancestry, and the first 10 principal components. *P* values of European ancestry and African American ancestry cohorts are adjusted for age, sex, and the first 10 principal components. The prevalence of rupture, severe atherosclerosis, calcification, thrombotic coronary artery disease (CAD), and CAD-associated death gradually increased with higher LDL-specific PRS quintiles. There were significantly more cases of plaque rupture ($P_{adjusted}$=0.002), severe atherosclerosis ($P_{adjusted}$<0.001), thrombotic CAD ($P_{adjusted}$=0.005), and CAD-associated death (*P*<0.001) within the highest LDL-specific PRS quintile in the overall cohort.

stent occlusion in the left circumflex artery (Figure 3C). PRS evaluation places him in the highest quintile for LDL-specific PRS and the third quintile for triglyceride-specific PRS. Case 2 is a 46-year-old male of self-reported European ancestry with no documented medical history. Histological examination shows plaque rupture in the mid-left circumflex (Figure 3D and 3E) and a large necrotic core in the mid-left anterior descending artery (Figure 3F and 3G). The subject was in the highest quintile for triglyceride-specific PRS and the third quintile for LDL-specific PRS.

DISCUSSION

Association Between Lipid PRS and Plaque Rupture or Erosion

This study is the first to investigate the relationship between lipid PRSs and histopathologic findings in a large-scale autopsy registry. Notably, LDL-specific PRS was significantly associated with higher odds of plaque rupture but not with plaque erosion in the overall cohort. Similarly, triglyceride-specific PRS tended to be related to higher odds of plaque rupture but not with plaque erosion. Plaque rupture, the leading cause of ACS, accounts for 60% to 65% of cases of sudden coronary death.[20] It results from the disruption of the fibrous cap and subsequent luminal thrombus formation, caused by the exposure of highly thrombogenic necrotic core to flowing blood.[20,23] The precursor lesion is a thin-cap fibroatheroma, characterized by a large necrotic core with infiltration of macrophages and T lymphocytes.[24] Because the formation of the necrotic core is predominantly driven by circulating lipid particles, it is reasonable that lipid PRS is strongly associated with the occurrence of plaque rupture. In contrast, the pathogenesis of plaque erosion, the second leading cause of thrombotic CAD, accounting for 30% to 35% of cases, remains poorly understood. Plaque erosion is pathologically defined by endothelial

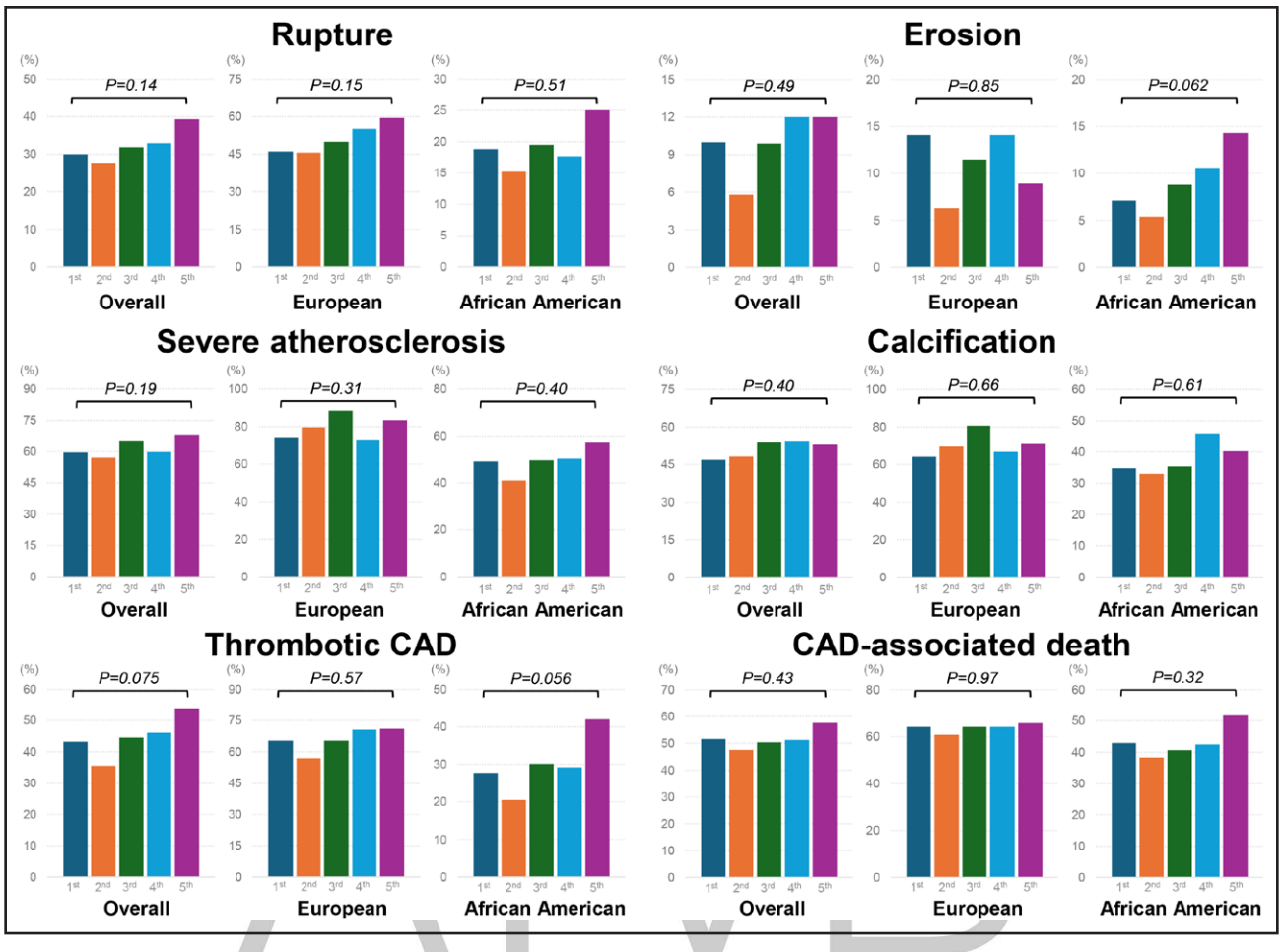

Figure 2. Association between triglyceride (TG)-specific PRS and histopathologic features.
The vertical bars represent the prevalence. Logistic regression analysis was used to compare the highest and lowest TG-specific polygenic risk score (PRS) quintiles. *P* values in the overall cohort are adjusted for age, sex, self-reported ancestry, and the first 10 principal components. *P* values of European ancestry and African American ancestry cohorts are adjusted for age, sex, and the first 10 principal components. The prevalence of rupture, severe atherosclerosis, and thrombotic coronary artery disease (CAD) gradually increased with higher TG-specific PRS quintiles, albeit without statistical significance.

denudation with an intact fibrous cap. The underlying lesion is typically less advanced (ie, pathological intimal thickening or fibroatheroma) compared with plaque rupture.[20] Key mechanisms implicated in endothelial damage in plaque erosion include altered endothelial shear stress, cigarette smoking, and vasospasm.[25–28] Our findings are, therefore, in line with the distinct pathogenesis of plaque erosion compared with plaque rupture, which is characterized by advanced atherosclerosis and lipid-associated features. Notably, our previous study demonstrated that CAD-related PRS is significantly associated with plaque rupture but not with plaque erosion,[10] suggesting that current genetic risk profiles for CAD predominantly reflect the biology of plaque rupture. These results underscore the need to identify genetic variants specifically associated with plaque erosion. Studies in our laboratory are underway, examining distinct pathways related to endothelial integrity and adhesion as potential causes of plaque erosion, but further work is needed to substantiate these hypotheses.

Associations Between PRS for Different Lipid Traits and Histopathologic Findings

Clinical and experimental studies have consistently demonstrated a strong association between elevated LDL-C levels and the development of atherosclerotic cardiovascular disease.[3,29,30] Mendelian randomization studies further support a causal and dose-dependent relationship between lifelong LDL-C exposure and atherosclerotic cardiovascular disease risk.[3] Although the association of hypertriglyceridemia with atherosclerotic disease is less pronounced, it has also been linked to adverse clinical outcomes, independent of LDL-C levels.[31,32] This residual cardiovascular risk is further supported by Mendelian randomization studies that have identified a causal link between elevated remnant cholesterol, a key pathogenic component of hypertriglyceridemia, and ischemic heart disease.[33,34]

In our cohort, subjects in the highest LDL-specific PRS quintile showed association with 2.11-fold higher odds

Table 4. Association of LDL-Specific PRS and Histopathologic Findings (Logistic Regression Analysis per SD Increase)

	Adjusted OR	95% CI	*P* value	Heterogeneity *P* value
Rupture				
European ancestry cohort	1.25	1.01–1.55	0.042	
African American ancestry cohort	1.18	0.92–1.51	0.20	
Overall cohort	1.22	1.04–1.43	0.017	0.71
Erosion				
European ancestry cohort	0.98	0.69–1.38	0.89	
African American ancestry cohort	1.07	0.79–1.46	0.65	
Overall cohort	1.03	0.82–1.30	0.80	0.68
TCFA				
European ancestry cohort	1.10	0.87–1.40	0.41	
African American ancestry cohort	0.92	0.68–1.26	0.61	
Overall cohort	1.03	0.86–1.25	0.74	0.35
Calcification				
European ancestry cohort	1.35	1.03–1.77	0.029	
African American ancestry cohort	0.97	0.78–1.19	0.76	
Overall cohort	1.10	0.93–1.30	0.27	0.048
Severe atherosclerosis				
European ancestry cohort	1.50	1.11–2.02	0.008	
African American ancestry cohort	1.26	1.03–1.54	0.023	
Overall cohort	1.33	1.13–1.57	<0.001	0.32
Thrombotic CAD				
European ancestry cohort	1.26	1.01–1.59	0.042	
African American ancestry cohort	1.16	0.94–1.44	0.16	
Overall cohort	1.21	1.04–1.41	0.016	0.60
CAD-associated death				
European ancestry cohort	1.29	1.03–1.61	0.026	
African American ancestry cohort	1.33	1.09–1.61	0.005	
Overall cohort	1.31	1.13–1.52	<0.001	0.85

Odds per SD increase in PRS. Adjusted for age, sex, body mass index, and the first 10 principal components. CAD indicates coronary artery disease; LDL, low-density lipoprotein; OR, odds ratio; PRS, polygenic risk score; and TCFA, thin-cap fibroatheroma.

of plaque rupture, 2.56-fold higher odds of ≥75% lumen narrowing, 1.92-fold higher odds of thrombotic CAD, and 2.3-fold higher odds of CAD-related death compared with those in the lowest quintile. Triglyceride-specific PRS was also associated with 1.64-fold higher odds of thrombotic CAD. These findings align with prior evidence suggesting that while genetic predisposition to elevated LDL-C exerts a more pronounced impact on various CAD phenotypes, the genetic risk associated with elevated triglycerides also contributes to CAD pathogenesis. This emphasizes the importance of addressing both LDL-C and triglycerides to comprehensively mitigate cardiovascular risk.

Clinical Utility of Lipid PRS

A previous study demonstrated that LDL PRS was associated with ischemic heart disease risk to a comparable extent as directly measured LDL-C levels.[35] Unlike single-timepoint blood lipid measurements, which may occasionally misclassify cardiovascular risk, PRS provides an estimate of an individual's cumulative lifelong exposure to elevated LDL-C or triglyceride levels. Because genetic predisposition is inherent and can be assessed at any age, PRS enables early identification of individuals at heightened risk before traditional clinical risk factors emerge. This early risk stratification provides an opportunity for behavioral modifications that may help mitigate disease progression.[9,36] From a pathological perspective, lipid-rich plaque and necrotic core formation occur silently and do not invariably lead to lumen narrowing, owing to positive remodeling.[37] Consequently, clinical symptoms may remain absent until the precipitating event of ACS. These findings suggest the potential value of early risk stratification through genetic risk

Table 5. Association of TG-Specific PRS and Histopathologic Findings (Logistic Regression Analysis per SD Increase)

	Adjusted OR	95% CI	*P* value	Heterogeneity *P* value
Rupture				
European ancestry cohort	1.20	0.96–1.49	0.10	
African American ancestry cohort	1.09	0.86–1.38	0.47	
Overall cohort	1.15	0.98–1.35	0.091	0.56
Erosion				
European ancestry cohort	1.02	0.72–1.43	0.93	
African American ancestry cohort	1.26	0.93–1.71	0.14	
Overall cohort	1.14	0.91–1.44	0.25	0.35
TCFA				
European ancestry cohort	0.91	0.71–1.16	0.44	
African American ancestry cohort	1.08	0.79–1.48	0.61	
Overall cohort	0.97	0.80–1.18	0.77	0.37
Calcification				
European ancestry cohort	1.05	0.81–1.37	0.69	
African American ancestry cohort	1.14	0.93–1.40	0.22	
Overall cohort	1.10	0.94–1.30	0.23	0.64
Severe atherosclerosis				
European ancestry cohort	1.16	0.88–1.53	0.30	
African American ancestry cohort	1.14	0.94–1.38	0.19	
Overall cohort	1.14	0.98–1.34	0.10	0.91
Thrombotic CAD				
European ancestry cohort	1.18	0.94–1.48	0.16	
African American ancestry cohort	1.22	0.99–1.50	0.060	
Overall cohort	1.20	1.03–1.40	0.020	0.82
CAD-associated death				
European ancestry cohort	1.08	0.86–1.35	0.52	
African American ancestry cohort	1.16	0.96–1.40	0.12	
Overall cohort	1.12	0.97–1.30	0.11	0.62

Odds per SD increase in PRS. Adjusted for age, sex, body mass index, and the first 10 principal components. CAD indicates coronary artery disease; OR, odds ratio; PRS, polygenic risk score; TCFA, thin-cap fibroatheroma; and TG, triglyceride.

assessment, coupled with lipid-lowering interventions before symptom onset, in helping to mitigate cardiovascular risk. Furthermore, PRS can identify individuals who may benefit significantly from pharmacological interventions, such as statins or PCSK9 inhibitors.[38–41] These insights highlight the clinical utility of PRS in facilitating early, personalized risk assessment and guiding treatment strategies tailored to the individuals.[38]

Limitations

This study has several limitations. First, because our data set consists solely of sudden death cases, caution is needed when applying these findings to the general clinical population. Second, the relatively small sample size may limit our ability to detect statistically significant associations between triglyceride-specific PRS and certain plaque phenotypes although it should be emphasized that clinical studies cannot provide such detailed insights into specific plaque phenotypes. Our findings would be better supported if validated in independent cohorts; however, to our knowledge, no existing studies combine genome-wide genotyping with systematic classification of distinct ACS plaque phenotypes. Future studies in larger and more diverse cohorts will be important to confirm the robustness and generalizability of our results.

Third, because DNA was extracted from FFPE tissues obtained at autopsy, DNA fragmentation, and crosslinking inherent to the fixation and embedding process substantially compromised DNA integrity. As a result, a large proportion of samples did not pass the rigorous QC thresholds required for genome-wide genotyping and were excluded from the final analysis.

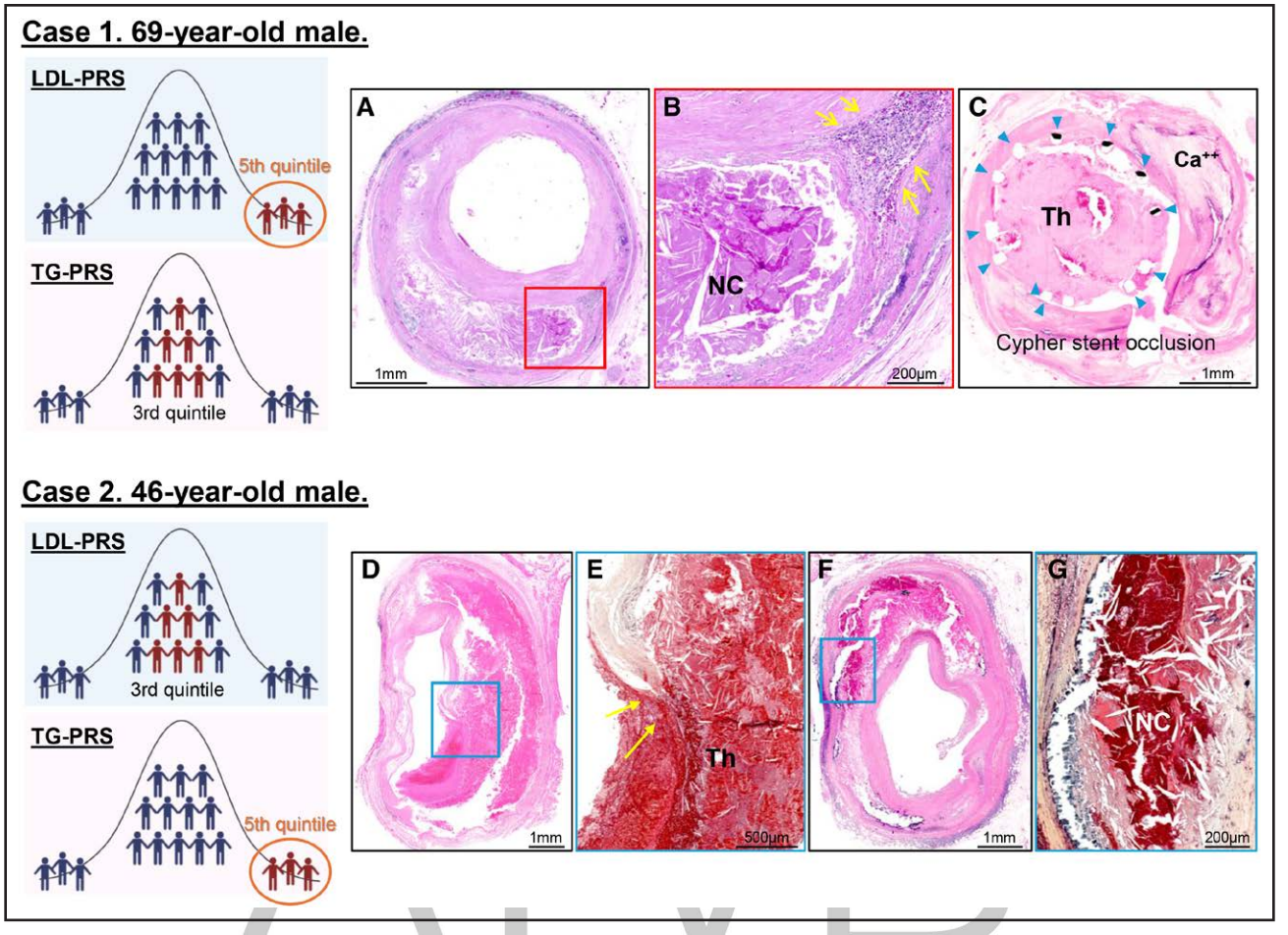

Figure 3. Representative cases showing the association between lipid polygenic risk score (PRS) and the histological findings of sudden coronary death subjects.

Case 1: 69-year-old male with self-reported European ancestry, within the highest LDL (low-density lipoprotein)–specific PRS quintile and the third triglyceride (TG)-specific PRS quintile. **A**, Histological image of the proximal left circumflex artery showing a large necrotic core (NC). **B**, High-power image of the red-boxed area from **A**, indicating NC and inflammatory cell infiltration at the edge of the NC (yellow arrows). **C**, Thrombotic occlusion (Th) of a Cypher stent implanted in the mid-left circumflex artery, on the surface of a fibrocalcific plaque (Ca^{++}). Blue arrowheads indicate stent struts. Case 2: 46-year-old male with self-reported European ancestry, within the highest TG-specific PRS quintile and the third LDL-specific PRS quintile. **D**, Histological image of the mid-left circumflex artery showing plaque rupture and acute thrombus. **E**, High-power image of the blue-boxed area from **D**, where yellow arrows indicate disruption of the fibrous cap. **F**, Low-power image of the mid-left anterior descending artery showing a large necrotic core and intraplaque hemorrhage. **G**, High-power image of the blue-boxed area from **F** showing a large necrotic core. **A** through **D** and **F** were stained with hematoxylin and eosin, while **E** and **G** were stained with Movat pentachrome.

Fourth, we lacked data on serum lipid levels because no blood samples were collected, which is common to other published genetic studies of lipid-related SNPs.[11] Furthermore, the correlation between lipid PRSs and measured lipid levels has been extensively validated in large-scale population studies. Therefore, our goal was not to replicate these findings but rather to extend them by investigating how lipid PRSs relate to distinct histopathologic phenotypes.

Fifth, selection bias may exist: individuals with European ancestry exhibited more advanced atherosclerotic features, possibly due to better survival after cardiovascular events linked to higher average socioeconomic status, despite individuals with African ancestry generally experiencing poorer outcomes.[42]

Sixth, because most GWASs to date have predominantly included individuals of European ancestry, PRSs generally perform better in European than in African ancestry.[7] In this study, we used trans-ancestry summary GWAS results from the Global Lipids Genetics Consortium, as prior work demonstrated that trans-ancestry PRS can provide similar or even greater predictive power for LDL-C compared with ancestry-specific PRS. For example, PRS generated from European and admixed African American GWAS accounted for 12% of the variation in LDL-C levels in Black compared with only 7% to 8% for PRS generated from European GWAS only. However, we acknowledge that the original GWAS included a substantially larger proportion of European than African ancestry participants, and therefore, the predictive

performance may be greater in our European ancestry cohort than in our African American ancestry cohort. Indeed, the stronger association of LDL PRS with plaque rupture observed in our European ancestry cohort compared with our African American ancestry cohort, despite the larger sample size of the latter, could reflect this ancestry-specific difference in predictive performance. These results underscore the need for larger GWAS of LDL-C and related traits in non-European populations to enhance PRS transferability and predictive accuracy across ancestries.

Last, clinical information was limited as it was obtained from the Office of the Chief Medical Examiner records. The observed prevalence of dyslipidemia was lower than expected though this may reflect underrecognition; a previous study found that only 24.6% of individuals with polygenic hypercholesterolemia reported a history of high cholesterol at enrollment.[43] In addition, our findings support the potential role of lipid PRS in identifying at-risk individuals who remain undiagnosed.

Conclusions

This autopsy study is the first to reveal associations between lipid PRS and specific histopathologic features of CAD. High LDL-specific PRS correlated with plaque rupture, ≥75% lumen area narrowing, thrombotic CAD, and CAD-related death but not with plaque erosion. In contrast, high triglyceride-specific PRS was significantly associated with thrombotic CAD and showed a trend toward association with plaque rupture but showed no link to plaque erosion. These findings provide mechanistic insights into the distinct mechanisms underlying these plaque phenotypes. Early risk stratification and targeted intervention based on lipid PRSs could help prevent plaque progression and rupture-mediated sudden cardiac death. Further studies are warranted to determine whether plaque erosion has a genetic basis and to inform targeted therapies for this specific cause of ACS.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4
Figures S1–S4

REFERENCES

1. Ahmad FB, Anderson RN. The leading causes of death in the US for 2020. *JAMA*. 2021;325:1829–1830. doi: 10.1001/jama.2021.5469
2. Wilson PW. Established risk factors and coronary artery disease: the Framingham Study. *Am J Hypertens*. 1994;7:7S–12S. doi: 10.1093/ajh/7.7.7s
3. Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, Daemen MJ, Demer LL, Hegele RA, Nicholls SJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2020;41:2313–2330. doi: 10.1093/eurheartj/ehz962
4. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;393:407–415. doi: 10.1016/s0140-6736(18)31942-1
5. Cadby G, Melton PE, McCarthy NS, Giles C, Mellett NA, Huynh K, Hung J, Beilby J, Dubé M-P, Watts GF, et al. Heritability of 596 lipid species and genetic correlation with cardiovascular traits in the Busselton Family Heart Study. *J Lipid Res*. 2020;61:537–545. doi: 10.1194/jlr.RA119000594
6. Nustad HE, Page CM, Reiner AH, Zucknick M, LeBlanc M. A Bayesian mixed modeling approach for estimating heritability. *BMC Proc*. 2018;12:31. doi: 10.1186/s12919-018-0131-z
7. Graham SE, Clarke SL, Wu KH, Kanoni S, Zajac GJM, Ramdas S, Surakka I, Ntalla I, Vedantam S, Winkler TW, et al; VA Million Veteran Program. The power of genetic diversity in genome-wide association studies of lipids. *Nature*. 2021;600:675–679. doi: 10.1038/s41586-021-04064-3
8. Trinder M, Li X, DeCastro ML, Cermakova L, Sadananda S, Jackson LM, Azizi H, Mancini GBJ, Francis GA, Frohlich J, et al. Risk of premature atherosclerotic disease in patients with monogenic versus polygenic familial hypercholesterolemia. *J Am Coll Cardiol*. 2019;74:512–522. doi: 10.1016/j.jacc.2019.05.043
9. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016;375:2349–2358. doi: 10.1056/NEJMoa1605086
10. Cornelissen A, Gadhoke NV, Ryan K, Hodonsky CJ, Mitchell R, Bihlmeyer NA, Duong TV, Chen Z, Dikongue A, Sakamoto A, et al. Polygenic risk score associates with atherosclerotic plaque characteristics at autopsy. *Arterioscler Thromb Vasc Biol*. 2024;44:300–313. doi: 10.1161/ATVBAHA.123.319818
11. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet*. 2013;45:1345–1352. doi: 10.1038/ng.2795
12. Karalis DG. Intensive lowering of low-density lipoprotein cholesterol levels for primary prevention of coronary artery disease. *Mayo Clin Proc*. 2009;84:345–352. doi: 10.1016/S0025-6196(11)60544-2
13. Marston NA, Giugliano RP, Im K, Silverman MG, O'Donoghue ML, Wiviott SD, Ference BA, Sabatine MS. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-regression analysis of randomized controlled trials. *Circulation*. 2019;140:1308–1317. doi: 10.1161/CIRCULATIONAHA.119.041998
14. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary

disease who died suddenly. *N Engl J Med*. 1997;336:1276–1282. doi: 10.1056/NEJM199705013361802
15. Burke AP, Farb A, Pestaner J, Malcom GT, Zieske A, Kutys R, Smialek J, Virmani R. Traditional risk factors and the incidence of sudden coronary death with and without coronary thrombosis in blacks. *Circulation*. 2002;105:419–424. doi: 10.1161/hc0402.102952
16. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, Maller J, Sklar P, de Bakker PIW, Daly MJ, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559–575. doi: 10.1086/519795
17. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR; 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature*. 2015;526:68–74. doi: 10.1038/nature15393
18. Ashar FN, Mitchell RN, Albert CM, Newton-Cheh C, Brody JA, Müller-Nurasyid M, Moes A, Meitinger T, Mak A, Huikuri H, et al. A comprehensive evaluation of the genetic architecture of sudden cardiac arrest. *Eur Heart J*. 2018;39:3961–3969. doi: 10.1093/eurheartj/ehy474
19. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, Vrieze SI, Chew EY, Levy S, McGue M, et al. Next-generation genotype imputation service and methods. *Nat Genet*. 2016;48:1284–1287. doi: 10.1038/ng.3656
20. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262–1275. doi: 10.1161/01.atv.20.5.1262
21. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193–202. doi: 10.1016/j.jacc.2006.03.042
22. Kolodgie FD, Burke AP, Farb A, Gold HK, Yuan J, Narula J, Finn AV, Virmani R. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol*. 2001;16:285–292. doi: 10.1097/00001573-200109000-00006
23. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R. Concept of vulnerable/unstable plaque. *Arterioscler Thromb Vasc Biol*. 2010;30:1282–1292. doi: 10.1161/ATVBAHA.108.179739
24. Kawai K, Kawakami R, Finn AV, Virmani R. Differences in stable and unstable atherosclerotic plaque. *Arterioscler Thromb Vasc Biol*. 2024;44:1474–1484. doi: 10.1161/ATVBAHA.124.319396
25. Chiu JJ, Chien S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. *Physiol Rev*. 2011;91:327–387. doi: 10.1152/physrev.00047.2009
26. Satta S, Beal R, Smith R, Luo X, Ferris GR, Langford-Smith A, Teasdale J, Ajime TT, Serré J, Hazell G, et al. A Nrf2-OSGIN1&2-HSP70 axis mediates cigarette smoke-induced endothelial detachment: implications for plaque erosion. *Cardiovasc Res*. 2023;119:1869–1882. doi: 10.1093/cvr/cvad022
27. Shin ES, Ann SH, Singh GB, Lim KH, Yoon HJ, Hur SH, Her AY, Koo BK, Akasaka T. OCT-defined morphological characteristics of coronary artery spasm sites in vasospastic angina. *JACC Cardiovasc Imaging*. 2015;8:1059–1067. doi: 10.1016/j.jcmg.2015.03.010
28. Hamana T, Shah P, Grogan A, Kawakami R, Williams D, Diaz KM, Virmani R, Finn AV. Risk factors favoring plaque erosion. *Curr Atheroscler Rep*. 2024;27:17. doi: 10.1007/s11883-024-01262-y
29. Navarese EP, Robinson JG, Kowalewski M, Kolodziejczak M, Andreotti F, Bliden K, Tantry U, Kubica J, Raggi P, Gurbel PA. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA*. 2018;319:1566–1579. doi: 10.1001/jama.2018.2525
30. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell*. 2015;161:161–172. doi: 10.1016/j.cell.2015.01.036
31. Ginsberg HN, Packard CJ, Chapman MJ, Borén J, Aguilar-Salinas CA, Averna M, Ference BA, Gaudet D, Hegele RA, Kersten S, et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. *Eur Heart J*. 2021;42:4791–4806. doi: 10.1093/eurheartj/ehab551
32. Raposeiras-Roubin S, Rosselló X, Oliva B, Fernández-Friera L, Mendiguren JM, Andrés V, Bueno H, Sanz J, Martínez de Vega V, Abu-Assi E, et al. Triglycerides and residual atherosclerotic risk. *J Am Coll Cardiol*. 2021;77:3031–3041. doi: 10.1016/j.jacc.2021.04.059
33. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;61:427–436. doi: 10.1016/j.jacc.2012.08.1026
34. Varbo A, Benn M, Tybjærg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation*. 2013;128:1298–1309. doi: 10.1161/CIRCULATIONAHA.113.003008
35. Wu H, Forgetta V, Zhou S, Bhatnagar SR, Paré G, Richards JB. Polygenic risk score for low-density lipoprotein cholesterol is associated with risk of ischemic heart disease and enriches for individuals with familial hypercholesterolemia. *Circ Genom Precis Med*. 2021;14:e003106. doi: 10.1161/CIRCGEN.120.003106
36. Arnold N, Koenig W. Polygenic risk score: clinically useful tool for prediction of cardiovascular disease and benefit from lipid-lowering therapy? *Cardiovasc Drugs Ther*. 2021;35:627–635. doi: 10.1007/s10557-020-07105-7
37. Otsuka F, Joner M, Prati F, Virmani R, Narula J. Clinical classification of plaque morphology in coronary disease. *Nat Rev Cardiol*. 2014;11:379–389. doi: 10.1038/nrcardio.2014.62
38. O'Sullivan JW, Raghavan S, Marquez-Luna C, Luzum JA, Damrauer SM, Ashley EA, O'Donnell CJ, Willer CJ, Natarajan P; American Heart Association Council on Genomic and Precision Medicine; Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease. Polygenic risk scores for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2022;146:e93–e118. doi: 10.1161/CIR.0000000000001077
39. Natarajan P, Young R, Stitziel NO, Padmanabhan S, Baber U, Mehran R, Sartori S, Fuster V, Reilly DF, Butterworth A, et al. Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting. *Circulation*. 2017;135:2091–2101. doi: 10.1161/CIRCULATIONAHA.116.024436
40. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield M, Devlin JJ, Nordio F, Hyde C, Cannon CP, Sacks F, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. *Lancet*. 2015;385:2264–2271. doi: 10.1016/S0140-6736(14)61730-X
41. Marston NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, Pedersen TR, Keech AC, Wang H, Lira Pineda A, et al. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score: results from the FOURIER trial. *Circulation*. 2020;141:616–623. doi: 10.1161/CIRCULATIONAHA.119.043805
42. Leigh JA, Alvarez M, Rodriguez CJ. Ethnic minorities and coronary heart disease: an update and future directions. *Curr Atheroscler Rep*. 2016;18:9. doi: 10.1007/s11883-016-0559-4
43. Trinder M, Francis GA, Brunham LR. Association of monogenic vs polygenic hypercholesterolemia with risk of atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2020;5:390–399. doi: 10.1001/jamacardio.2019.5954