JACC: ASIA VOL. 4, NO. 6, 2024

STATE-OF-THE-ART REVIEW

Management of Coronary Vulnerable Plaque With Medical Therapy or Local Preventive Percutaneous Coronary Intervention

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ABSTRACT

Acute coronary syndromes (ACS) often result from the rupture or erosion of high-risk coronary atherosclerotic plaques (ie, vulnerable plaques). Advances in intracoronary imaging such as intravascular ultrasound, optical coherence tomography, or near-infrared spectroscopy have improved the identification of vulnerable plaques, characterized by large plaque burden, small minimal luminal area, thin fibrous cap, and large lipid content. Although pharmacology, including lipid-lowering agents, and intensive risk-factor control are pivotal for management of vulnerable plaques and secondary prevention, recurrent events tend to accrue despite intensive pharmacotherapy. Therefore, it has been hypothesized that local preventive percutaneous coronary intervention may passivate these vulnerable plaques, preventing the occurrence of plaque-related ACS. However, solid evidence is lacking on its use for treatment of non-flow-limiting vulnerable plaques. As such, the optimal management of vulnerable plaques has not been established. Herein, we have reviewed the diagnosis and management of vulnerable plaques, focusing on systematic pharmacology and focal treatments.
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Ischemic heart disease is the leading cause of death worldwide.[1,2] It is well known that angiographically severe or physiologically significant coronary artery disease (CAD) is associated with increased risks of acute coronary syndrome (ACS), myocardial infarction (MI), or sudden cardiac death.[3,4] However, despite successful revascularization of such significant coronary lesions and optimal medical therapy (OMT), there remains a substantial risk of recurrent ischemic events in nonculprit, angiographically mild-to-moderate narrowing, physiologically nonsignificant coronary lesions containing high-risk coronary plaques (so-called vulnerable plaques).[5-8] The majority of unexpected coronary events such as ACS or sudden cardiac deaths are caused by the rupture or erosion of atherosclerotic vulnerable coronary plaques.[9-11] These nonflow-limiting vulnerable plaques can be identified with intravascular coronary imaging;[5,6,12-16] High-risk vulnerable plaques are typically characterized by thin-cap fibroatheromas, a high lipid content, a large plaque burden, and a small luminal area.

Until recently, there has been no consensus on the optimal management of vulnerable coronary plaques,[17-19] and there are still unmet issues with regard to assessment, prevention, and treatment of vulnerable plaques. In particular, pharmacology (eg, lipid-lowering agents or antiplatelet drugs) and

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Jagat Narula, MD, PhD, served as Guest Associate Editor for this paper. Nathan Wong, PhD, served as Guest Editor-in-Chief for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 2, 2024; revised manuscript received March 20, 2024, accepted April 4, 2024.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2024.04.001

JACC: ASIA, VOL. 4, NO. 6, 2024
JUNE 2024:425–443

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CTA = computed tomography angiography

FFR = fractional flow reserve

IVUS = intravascular ultrasound

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

NIRS = near-infrared spectroscopy

OCT = optical coherence tomography

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

PCSK9 = proprotein convertase subtilisin kexin 9

RCT = randomized clinical trial

intensive risk-factor control is the cornerstone for the optimal management of nonflow-limiting vulnerable plaques. However, in patients with ACS or MI, recurrent events tend to accrue despite the implementation of secondary prevention measures with intensive pharmacotherapy. Therefore, it has been hypothesized that local preventive therapy of percutaneous coronary intervention (PCI) may passivate these vulnerable-plaque lesions, preventing the occurrence of plaque-related acute coronary events. Only a few studies have been conducted to examine the benefit of preventive PCI on vulnerable plaques.[20-23] In this review, we summarizes the current evidence on the detection and optimal management of vulnerable plaque with systemic pharmacology or local preventive therapy with PCI and future perspectives from ongoing randomized clinical trials (RCTs). This review primarily focuses on the optimal management of vulnerable coronary plaques in patients who have documented CAD or have experienced previous cardiac events, and the pathology, risk stratification, and genomics are not the primary focus of this review.

IDENTIFICATION OF VULNERABLE PLAQUES

The key findings of invasive and noninvasive imaging studies for the detection of vulnerable coronary plaques are summarized in **Table 1**.

INVASIVE IMAGING ASSESSMENT. Intravascular ultrasound. Coronary angiography has been the gold standard for diagnosing CAD and assessing lesion severity. However, coronary angiography only provides information about the lumenogram. By contrast, grayscale intravascular ultrasound (IVUS) can provide more detailed anatomical information that allows quantitative determination of the vessel and lumen dimensions and distribution, morphology, and severity of atherosclerotic coronary plaque.[24-26] Furthermore, plaque composition can be assessed with various postprocessing methods, such as virtual histology intravascular ultrasound (VH-IVUS) and integrated backscatter intravascular ultrasound (IB-IVUS)[26]; coronary plaque can be subclassified into 4 types: fibrous, fibrofatty, necrotic core, and dense calcium.[27]

The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study was the first large prospective study to identify characteristics of vulnerable plaque using grayscale and VH-IVUS and its association with future coronary events.[5] A total of 697 patients with ACS underwent 3-vessel angiography and grayscale and radiofrequency IVUS evaluation for nonculprit lesions after successful culprit-lesion PCI. During a median follow-up of 3.4 years, 20.4% of patients experienced recurrent major adverse cardiovascular events (MACE) (a composite of death from cardiac causes, cardiac arrest, MI, or rehospitalization caused by unstable or progressive angina), of which 12.9% were related to PCI-treated culprit lesions and 11.6% were related to nonculprit lesions. Most event cases were derived from rehospitalizations for unstable or progressive angina, and serious cardiovascular events of cardiac death, cardiac arrest, or MI were less common. The characteristics of the vulnerable plaque responsible for nonculprit lesion-related MACE identified by VH-IVUS were a plaque burden of at least 70%, a minimal luminal area (MLA) of $\leq$4.0 mm^2, and the presence of thin-cap fibroatheroma (TCFA). A plaque burden of $\geq$70% was the strongest predictor of MACE, followed by the presence of TCFA and MLA $\leq$4.0 mm^2. Such imaging characteristics of vulnerable plaques associated with an increased risk of clinical events were validated in subsequent imaging studies, including the VIVA (Virtual Histology in Vulnerable Atherosclerosis) and the ATHEROREMO-IVUS (European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis - Intravascular Ultrasound) studies.[12,13]

Optical coherence tomography. Optical coherence tomography (OCT) uses light rather than ultrasound to generate an image with higher resolution (more than 10×) than IVUS, which enables a more clear visualization of TCFA (cap thickness <65 μm).[28,29] However, because of a reduced tissue penetration compared with IVUS, OCT provides less delineation of the outer vessel boundary and a less reliable quantitative assessment of atherosclerotic plaque volume.[27] The CLIMA (Relationship Between Coronary Plaque Morphology of the Left Anterior Descending Artery and 12 Months Clinical Outcomes) study assessed whether the presence of OCT-predefined high-risk features (MLA, fibrous cap thickness, lipid arc circumferential extension, and macrophage infiltration) is associated with the future risk of MI or cardiac death in 1,003 patients who underwent OCT evaluation of an untreated proximal left anterior descending coronary artery (LAD).[30] Four different

OCT high-risk features, an MLA <3.5 mm^2, a fibrous cap thickness <75 μm, a lipid arc circumferential extension >180°, and a macrophage infiltration were associated with an increased risk of cardiac death and target-segment MI at 1 year. Another study including 1,378 patients who underwent OCT for nonculprit plaques[31] assessed the association between lipid-rich plaque and TCFA by OCT and the risk of subsequent ACS event. During a median 6 years of follow-up, patients with high-risk features of both lipid-rich plaque and TCFA were associated with more than 10× risk of subsequent ACS compared with those without these features.

The COMBINE OCT-FFR (Combined Optical Coherence Tomography and Fractional Flow Reserve Assessment to Better Predict Adverse Event Outcomes in DM Patients) trial evaluated the impact of OCT-detected TCFA in fractional flow reserve (FFR)-negative lesions on adverse clinical events.[8] Diabetic patients who were presented with either stable CAD or ACS and had FFR-negative lesions (angiographic diameter stenosis [DS] of 40%-80%) were evaluated. Among 390 patients who had ≥1 FFR-negative lesion, 98 (25%) had TCFA-positive lesions and 292 (75%) had TCFA-negative lesions. During 18 months, the primary composite endpoints of cardiac death, target-vessel MI, clinically-driven target-lesion revascularization, or unstable angina requiring hospitalization more frequently occurred in the TCFA-positive group than in the TCFA-negative group (13.3% vs 3.1%, respectively; HR: 4.65; 95% CI: 1.99 to 10.89), most of which were attributable to clinically driven target-lesion revascularization or unstable angina requiring hospitalization.

In a recent OCT study,[32] a total of 883 AMI patients were evaluated with OCT of all 3 main epicardial coronary arteries after culprit-lesion PCI. During a median 3.3 years, the incidence of the primary composite endpoint (cardiac death, nonculprit lesion-related nonfatal MI, and unplanned coronary revascularization) was 7.2%. Both TCFA (adjusted HR 3.05; 95% CI: 1.67-5.57) and smaller MLA <3.5 mm^2 (adjusted HR: 3.71; 95% CI 1.22-11.34 in patient-level analysis) were independent predictors of the primary endpoint. Similarly, in the PECTUS-obs (Identification of Risk Factors for Acute Coronary Events by OCT After STEMI and NSTEMI in Patients With Residual Non-flow Limiting Lesions) study,[33] OCT-identified high-risk plaque in nonflow-limiting (FFR >0.80) nonculprit lesions was associated with an increased risk of adverse clinical events.

Near-infrared spectroscopy. Near-infrared spectroscopy (NIRS) was developed to accurately identify the lipid core in plaques.[34] NIRS can be used to detect lipid-core plaque because cholesterol-rich atherosclerotic plaques have a specific NIRS chemical signature.[34] The lipid core burden index (LCBI) is the fraction of pixels with probability of lipid >0.6 divided by all analyzable pixels within the region of interest, multiplied by 1,000. $MaxLCBI_{4mm}$ is defined as the maximum LCBI within any 4-mm pull back length across the target lesion. The LRP (Lipid-Rich Plaques) study examined the relationship between lipid-rich plaques detected by NIRS-IVUS at unstented sites and subsequent coronary events.[15] Of 1,271 patients with an analyzable $maxLCBI_{4mm}$, the 2-year incidence of nonculprit-related major adverse cardiovascular events (NC-MACE) was 9%. The HR for NC-MACE was 1.21 (95% CI: 1.09-1.35) for each 100-unit increase in $maxLCBI_{4mm}$. Among patients with a $maxLCBI_{4mm}$ >400, the unadjusted and adjusted HRs for NC-MACE were 2.18 (95% CI: 1.48-3.22) and 1.89 (95% CI: 1.26-2.83), respectively. In the PROSPECT II (Providing Regional Observations to Study Predictors of Events in the Coronary Tree II) study,[6] 898 patients with a recent MI were enrolled after successful intervention for all flow-limiting lesions, for whom 3-vessel imaging with combined NIRS and IVUS evaluations were conducted to identify high-risk plaques. During a median follow-up of 3.7 years, 66 (8.0%) events were noted from untreated nonculprit lesions, and a $maxLCBI_{4mm}$ ≥324.7 (adjusted OR: 2.27; 95% CI: 1.25-4.13) and plaque burden ≥70% (adjusted OR: 7.83; 95% CI: 4.12-14.89) were independent predictors of nonculprit lesion-related MACE.

NONINVASIVE IMAGING ASSESSMENT. Coronary computed tomography angiography. Several coronary computed tomography angiography (CTA) studies have identified characteristics of vulnerable plaque, including positive remodeling, low-attenuation plaques, spotty calcification, and a napkin-ring sign.[35-38] In a post hoc analysis of the SCOT-HEART (Scottish Computed Tomography of the HEART) trial including 1,769 patients experiencing stable chest pain, the low-attenuation plaque burden detected by coronary CTA was the strongest predictor of future MI during a median follow-up of 4.7 years.[37] In another prospective study including 895 patients who were followed for more than 1 year for an ACS event, the napkin-ring sign detected on coronary CTA was strongly associated with development of ACS events, which were independent of other coronary CTA features, such as positive remodeling and low attenuation plaque.[38] In a combined imaging study using coronary CTA and VH-IVUS, lesions with positive remodeling on coronary CTA were associated with vulnerable plaque on VH-IVUS containing TCFA and a higher necrotic

TABLE 1 Summary of the Results of the Invasive and Noninvasive Studies for Detection of Vulnerable Plaques

Study (Year)	Cohort (N)	Evaluation Method	Follow-Up Duration	Outcomes	The Characteristics of the Vulnerable Plaque
Invasive					
PROSPECT (2011)[5]	ACS (697)	Grayscale IVUS and RF-IVUS	Median 3.4 y	The 3-y cumulative rates of MACE were 12.9% of patients (related to culprit lesions) and 11.6% of patients (related to nonculprit lesions).	Plaque burden >70% (HR: 5.03; 95% CI: 2.51-10.11) or an MLA <4.0 mm^2 (HR: 3.21; 95% CI: 1.61-6.42) or TCFA (HR: 3.35; 95% CI: 1.77-6.36) were associated with nonculprit lesions associated recurrent events.
VIVA (2015)[17]	Stable CAD or ACS (170)	VH-IVUS	Median 1.7 y	18 MACE (composite of death, MI, or unplanned revascularization) occurred in 16 patients.	TCFA (HR: 7.53; 95% CI: 1.12-50.55) and plaque burden >70% (HR: 8.13; 95% CI: 1.63-40.56) were associated with nonculprit lesion-associated MACE.
ATHEROREMO-IVUS (2014)[18]	Stable CAD or ACS (581)	Grayscale IVUS and RF-IVUS	1-y outcome was evaluated	Cumulative Kaplan-Meier incidence of 1-y MACE (composite of mortality, ACS, or unplanned coronary revascularization) was 7.8%.	TCFA (adjusted HR: 1.98; 95% CI: 1.09-3.60) and plaque burden >70% (HR: 2.90; 95% CI: 1.60-5.25) were independently associated with a higher MACE rate.
CLIMA (2016)[30]	Stable CAD or ACS (1,003)	OCT	1-y outcome was evaluated	At 1-y, the primary endpoint (composite of cardiac death and target segment MI) was observed in 37 patients (3.7%).	MLA <3.5 mm^2 (HR: 2.1; 95% CI: 1.1-4.0), fibrous cap thickness <75 μm (HR: 4.7; 95% CI: 2.4-9.0), lipid arc circumferential extension >180° (HR: 2.4; 95% CI: 1.2-4.8), and OCT-defined macrophages (HR: 2.7; 95% CI: 1.2-6.1) were associated with increased risk of the primary endpoint.
Kubo et al (2021)[31]	ACS (1,378)	OCT	Median 6 y	72 ACS occurred from nonculprit lesions.	Both lipid-rich plaque and TCFA were associated with a higher risk of subsequent ACS compared with those without these characteristics (33% vs 2%; HR: 19.14; 95% CI: 11.74-31.20).
COMBINE OCT-FFR (2021)[8]	Stable CAD or ACS (390)	OCT	1.5-y outcome was evaluated	The incidences of primary endpoint (composite of cardiac mortality, target vessel MI, clinically driven target lesion revascularization or unstable angina requiring hospitalization at 18 mo) were 13.3% in TCFA-positive and 3.1% in TCFA-negative groups (HR: 4.65; 95% CI: 1.99-10.89).	TCFA was the strongest predictor of major adverse clinical events (HR: 5.12; 95% CI: 2.12-12.34).
Jiang et al (2023)[32]	Acute MI (883)	OCT	Median 3.3 y	The 4-y cumulative rate of the primary endpoint (composite of cardiac death, nonculprit lesion-related nonfatal MI, and unplanned coronary revascularization) was 7.2%.	Both TCFA (adjusted HR: 3.05; 95% CI: 1.67-5.57 in patent-level analysis) (adjusted HR: 8.15; 95% CI: 3.67-18.07 in lesion-level analysis) and MLA <3.5 mm^2 (adjusted HR: 3.71; 95% CI: 1.22-11.34 in patient-level analysis) (adjusted HR: 4.33; 95% CI: 1.81-10.38 in lesion-level analysis) were independent predictors of the primary endpoint.
PECTUS-obs (2023)[33]	Acute MI (438)	OCT	2-y outcome was evaluated	The incidences of primary endpoint (composite of all-cause mortality, nonfatal MI, or unplanned revascularization at 2 y) were 15.4% in patients with a high-risk plaque and 8.3% without a high-risk plaque (HR: 1.93; 95% CI: 1.08-3.47).	A lesion was deemed high-risk if it contained at least 2 of the following 3 prespecified criteria: 1) a lipid arc of at least 90°; 2) a minimal fibrous cap thickness of <65 μm; and 3) either plaque rupture or thrombus presence. The presence of a high-risk plaque was associated with 2-y MACE (HR: 1.99; 95% CI: 1.10-3.61).
LRP (2014)[15]	Known or suspected CAD (1,271)	NIRS-IVUS	Mean 1.9 y	The 2-y cumulative incidence of nonculprit MACE (composite of cardiac death, cardiac arrest, nonfatal MI, ACS, revascularization, and readmission for angina) was 9% (n = 103).	Among patients with a $maxLCBI_{4mm}$ of >400, the unadjusted and adjusted HRs for NC-MACE were 2.18 (95% CI: 1.48-3.22; $P < 0.0001$) and 1.89 (95% CI: 1.26-2.83; $P = 0.0021$), respectively.
PROSPECT II (2021)[6]	Recent MI (898)	NIRS-IVUS	Median 3.7 y	The incidence of MACE (composite of cardiac death, MI, unstable angina, or progressive angina) from untreated nonculprit lesions was 8.0% (n = 66).	A $maxLCBI_{4mm}$ of ≥ 324.7 (adjusted OR: 2.27; 95% CI: 1.25-4.13) and plaque burden of ≥ 70% (adjusted OR: 7.83; 95% CI: 4.12-14.89) were independent predictors of patient-level nonculprit lesion-related MACE.

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TABLE 1 Continued

Study (Year)	Cohort (N)	Evaluation Method	Follow-Up Duration	Outcomes	The Characteristics of the Vulnerable Plaque
Noninvasive					
SCOT-HEART (2020)[37]	Stable CAD (1,769)	coronary CTA	Median 4.7 y		The low-attenuation plaque burden detected by coronary CTA was the strongest predictor of future MI.
Otsuka et al (2013)[38]	Patients undergoing coronary CTA (895)	coronary CTA	Median 3.0 y	24 (2.7%) ACS events (cardiac death, nonfatal MI, or unstable angina) had occurred.	The napkin-ring sign detected on coronary CTA was strongly associated with development of ACS events, independent of other coronary CTA features, such as positive remodeling and low attenuation plaque.
Kröner et al (2011)[39]	Patients undergoing coronary CTA (45)	coronary CTA and VH-IVUS			Lesions with positive remodeling on coronary CTA are associated with increased levels of plaque vulnerability on VH-IVUS images including a higher percent necrotic core and a higher prevalence of TCFA.
3V FFR-FRIENDS (2019)[4]	Stable CAD or ACS (299)	Coronary CTA and coronary angiography with FFR	5-y outcome was evaluated		A lower FFR value and a higher number of high-risk plaque characteristics (MLA <4 mm^2, plaque burden ≥70%, low attenuating plaque, positive remodeling, napkin-ring sign, or spotty calcification) were associated with an increased risk of a vessel-oriented composite outcome.

ACS = acute coronary syndrome; CAD = coronary artery disease; CTA = coronary computed tomography angiography; FFR = fractional flow reserve; IVUS = intravascular ultrasound; LCBI = lipid core burden index; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; MLA = minimal luminal area; NIRS = near-infrared spectroscopy; OCT = optical coherence tomography; RF-IVUS = radiofrequency intravascular ultrasound; TCFA = thin cap fibroatheroma; VH-IVUS = virtual histology intravascular ultrasound.

core.[39] A subgroup analysis from the 3V FFR-FRIENDS (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and Its Clinical Impact in Patients With Coronary Artery Disease) study[4] evaluated the prognostic implications of coronary CTA-defined high-risk plaque characteristics according to physiological stenosis severity in 772 vessels from 299 patients who underwent both coronary CTA and invasive FFR assessment. This study evaluated the relationship of the presence and number of high-risk plaque characteristics (MLA <4 mm^2, plaque burden ≥70%, low attenuating plaque, positive remodeling, napkin-ring sign, or spotty calcification) stratified by FFR values with the risk of vessel-oriented composite outcome (a composite of vessel-related ischemia-driven revascularization, vessel-related MI, or cardiac death) at 5 years. A lower FFR value and a higher number of high-risk plaque characteristics were associated with an increased risk of a vessel-oriented composite outcome. Interestingly, in the FFR >0.80 group, lesions with ≥3 high-risk plaque characteristics were associated with a significantly higher risk of composite outcome, but in the FFR ≤0.80 group, there was no significant difference in the risk of composite outcome according to the presence or absence high-risk plaque characteristics.

However, prior coronary CTA studies merely reported the association of future events with the presence of high-risk plaque characteristics but did not attempt to attribute these events to specific vulnerable plaques. Therefore, the gold standard technique for detection of vulnerable plaques has not been conducted in the noninvasive imaging studies. Therefore, further research is necessary to provide better identification of which patients or lesions can mostly benefit from invasive or noninvasive imaging evaluation for detection of vulnerable plaques, optimal risk-stratification, and the application of preventive PCI or other preventive strategies.

TREATMENT OF CORONARY VULNERABLE PLAQUE

NONINVASIVE STRATEGY OF SYSTEMIC MEDICAL THERAPY. Systemic pharmacotherapies have become the cornerstone of atherosclerotic plaque stabilization to improve prognosis. From low-density lipoprotein-lowering drugs, such as statins and

TABLE 2 Summary of Randomized Trials and Observational Studies Regarding Lipid-Lowering Therapy for Patients With Vulnerable Plaque

Study (Year)	Cohort (N)	Comparison (N)	Evaluation Method	Therapy Duration (mo)	Change in LDL-C Levels (mg/dL)	Change in Plaque Burden, Fibrous Cap Thickness (mm), Lipid Arc (°), or MaxLCBI$_{4mm}$	Comparison in Clinical Outcomes
ACS							
ESTABLISH (2004)[42]	ACS (70)	Atorvastatin 20 mg/d (35) vs usual care (35)	IVUS	6	Atorvastatin vs usual care. Baseline 124.6 ± 34.5; follow-up 70.0 ± 25.0 vs baseline 123.9 ± 35.3; follow-up 119 ± 24.6 ($P < 0.0001$)	Atorvastatin vs usual care. Change in plaque volume (%): −13.1% ± 12.8% vs 8.7% ± 14.9% ($P < 0.0001$)	Atorvastatin vs usual care. No death or TV MI in either group. TVR: 24.2% vs 25.0% ($P = 0.8471$)
IBIS-4 (2015)[43]	STEMI (103)	Rosuvastatin 40 mg daily (103)	Grayscale IVUS and RF-IVUS	13	Baseline median 3.29 mmol/L; follow-up 1.89 mmol/L	Change in percent atheroma volume: −0.9% (95% CI: −1.56% to −0.96%; $P = 0.007$)	-
JAPAN-ACS (2009)[44]	ACS (307)	Pitavastatin 4 mg/d (153) vs atorvastatin 20 mg/d (154)	IVUS	8-12	Pitavastatin vs atorvastatin. Baseline 130.9 ± 33.3; follow-up 81.1 ± 23.4; percent change −36.2% ± 19.5% vs Baseline 133.8% ± 31.4%; follow-up 84.1% ± 27.4%; percent change −35.8% ± 22.9% ($P = 0.9$)	Pitavastatin vs atorvastatin. Change in plaque volume: −16.9% ± 13.9% vs −18.1 ± 14.2% ($P = 0.5$)	Pitavastatin vs atorvastatin. No death in either group. MI: 0 vs 3 (2.0%) ($P = 0.2$) TLR: 16 (10.9%) vs 19 (12.8%) ($P = 0.6$)
STABLE (2016)[45]	Stable CAD or ACS (312)	Rosuvastatin 40 mg/d (209) vs rosuvastatin 10 mg/d (103)	Grayscale IVUS and VH-IVUS	12	Rosuvastatin 40 mg/d vs rosuvastatin 10 mg/d. Baseline 105.3 ± 32.8; follow-up 59.1 ± 22.2 vs baseline 109.3 ± 40.9; follow-up 78.8 ± 27.8 ($P < 0.001$ for follow-up values)	Rosuvastatin 40 mg/d vs rosuvastatin 10 mg/d. Change in percent atheroma volume (%): −0.88 ± 0.40 vs −0.85 ± 0.38 ($P = 0.735$) Change in necrotic core volume: −3.72% ± 0.71% vs −2.17% ± 0.70% ($P = 0.223$) Change in fibrous volume: −0.07% ± 0.58% vs −0.34% ± 0.60% ($P = 0.793$) Change in fibrofatty volume: 3.80% ± 0.71% vs 1.69% ± 0.74% ($P = 0.097$) Change in dense calcium volume: −0.02% ± 0.35% vs 0.82% ± 0.37% ($P = 0.197$)	Rosuvastatin 40 mg/d vs rosuvastatin 10 mg/d. No death in either group. MACE: 3.9% vs 2.7% ($P > 0.05$)
EASY-FIT (2014)[46]	Unstable angina (70)	Atorvastatin 20 mg/d (35) vs atorvastatin 5 mg/d (35)	OCT	12	Atorvastatin 20 mg/d vs atorvastatin 5 mg/d. Baseline 127 (Q1, Q3: 111, 155); follow-up 69 (Q1, Q3: 61, 80) vs Baseline 117 (Q1, Q3: 110, 138); follow-up 78 (Q1, Q3: 66, 108) ($P < 0.05$ for follow-up values)	Atorvastatin 20 mg/d vs atorvastatin 5 mg/d. Change in fibrous cap thickness: 73 (Q1, Q3: 28, 113 μm) vs 19 (Q1, Q3: −1, 48 μm) Change in lipid arc: −50° (Q1, Q3: −60°, −30°) vs −10° (Q1, Q3: −20°, −5°)	No cardiac death or MI in either group.
ESCORT (2018)[47]	ACS (70)	Early pitavastatin 4 mg/d from baseline (35) vs late pitavastatin 4 mg/d after 3 wk from baseline (35)	OCT	9	Early statin group vs late statin group. Baseline 117 (Q1, Q3: 105, 129); 3-wk 63 (Q1, Q3: 58, 78) vs Baseline 118 (Q1, Q3: 109, 135); 3-wk 119 (Q1, Q3: 105, 138) ($P < 0.05$ for 3-wk values)	Early statin group vs Late statin group. Change in minimum fibrous-cap thickness: Baseline 140 μm (Q1, Q3: 120, 170 μm); 3-wk 160 μm (Q1, Q3: 130, 190 μm); 36-wk 230 μm (Q1, Q3: 170, 320 μm) vs Baseline 135 μm (Q1, Q3: 110, 183 μm); 3-wk 130 μm (Q1, Q3: 108, 160 μm); 36-wk 200 μm (Q1, Q3: 170, 260) μm ($P < 0.05$ for 3-wk values) Change in maximum lipid arc: Baseline 175° (Q1, Q3: 135°, 276°); 3-wk 180° (Q1, Q3: 133°, 263°); 36-wk 153° (Q1, Q3: 111°, 230°) vs Baseline 186° (Q1, Q3: 150°, 226°); 3-wk 181° (Q1, Q3: 152°, 216°); 36-wk 164° (Q1, Q3: 133°, 186°)	No cardiac death, TL MI, or TLR in either group.
PRECISE-IVUS (2015)[53]	Stable CAD or ACS (202)	Atorvastatin plus ezetimibe 10 mg/d (100) vs atorvastatin alone (102)	IVUS	9-12	Atorvastatin plus ezetimibe vs atorvastatin alone. Baseline 109.8 ± 25.4; follow-up 63.2 ± 16.3; percent change −40% ± 18% vs baseline 108.3% ± 26.3%; follow-up 73.3% ± 20.3%; percent change −29% ± 24% ($P < 0.001$)	Atorvastatin plus ezetimibe vs atorvastatin alone. Change in percent atheroma volume: −1.4% (−3.4% to −0.1%) vs −0.3% (−1.9% to 0.9%) ($P = 0.001$)	No death in either group and 1 MI in each group.

Continued on the next page

TABLE 2 Continued

Study (Year)	Cohort (N)	Comparison (N)	Evaluation Method	Therapy Duration (mo)	Change in LDL-C Levels (mg/dL)	Change in Plaque Burden, Fibrous Cap Thickness (mm), Lipid Arc (°), or MaxLCBI$_{4mm}$	Comparison in Clinical Outcomes
ZEUS (2014)[54]	ACS (95)	Atorvastatin 20 mg/d plus ezetimibe 10 mg/d (45) vs atorvastatin 20 mg/d alone (50)	IVUS	6	Atorvastatin plus ezetimibe vs atorvastatin alone. Baseline 116.2 ± 24.7; follow-up 56.8 ± 19.5; percent change −49.8% ± 19.9% vs baseline 114.3% ± 34.0; follow-up 70.3% ± 23.6; percent change −34.6% ± 27.3% ($P = 0.016$)	Atorvastatin plus ezetimibe vs atorvastatin alone. Change in plaque volume: −12.5% ± 12.6% vs −7.5% ± 12.6% ($P = 0.06$)	No death, MI, or stroke in either group. Atorvastatin plus ezetimibe vs atorvastatin alone. TLR: 12.0% vs 13.3% ($P = 0.84$)
OCTIVUS (2017)[55]	STEMI (87)	Atorvastatin 80 mg/d plus ezetimibe 10 mg/d (43) vs atorvastatin 80 mg/d plus placebo (44)	IVUS	12	Atorvastatin plus ezetimibe vs atorvastatin plus placebo. Baseline 3.7 ± 0.7 mmol/L; follow-up 1.4 ± 0.8 mmol/L; percent change −62.0 ± 19.2% vs baseline 4.1 ± 0.9 mmol/L; follow-up 2.0 ± 0.5 mmol/L; percent change −52.4 ± 10.9% ($P < 0.001$)	Atorvastatin plus ezetimibe vs atorvastatin plus placebo. Change in percent atheroma volume): −2.2% (Q1, Q3: −5.4% to 0.7%) vs −1.0% (Q1, Q3: −5.3% to 1.0%) ($P = 0.67$)	-
ODYSSEY J-IVUS (2019)[63]	ACS (206)	Alirocumab 75 mg every 2 wk plus statin (102) vs statin alone (104)	IVUS	9	Alirocumab plus statin vs statin alone. Percent change from baseline: −64.5% ± 1.8% vs −7.6% ± 1.9% ($P < 0.0001$)	Alirocumab plus statin vs statin alone. Change in total atheroma volume: −4.8% ± 1.0% vs −3.1% ± 1.0% ($P = 0.2279$)	Alirocumab plus statin vs statin alone. Death: 0 vs 1 (1.0%) MI: 2 (1.9%) vs 3 (2.9%) Revascularization: 4 (3.9%) vs 2 (2.0%)
HUYGENS (2022)[64]	NSTEMI (161)	Evolocumab 420 mg monthly (80) vs placebo (81)	OCT	12	Evolocumab vs placebo. Absolute change from baseline: −114.2 ± 41.7 vs −55.3 ± 47.1 ($P < 0.001$)	Evolocumab vs placebo. Change in minimum fibrous cap thickness from baseline: 39.0 μm (Q1, Q3: 20.5, 71.0 μm) vs 22.0 μm (Q1, Q3: 8.0, 36.0 μm) ($P = 0.015$) Change in maximum lipid arc from baseline: −51.0° (Q1, Q3: −99.0°, −20.5°) vs −25.0° (Q1, Q3: −72.0°, 4.0°) ($P = 0.04$)	Evolocumab vs placebo. Death: 0% vs 1.2% MI: 0% vs 3.7%
PACMAN-AMI (2022)[65]	STEMI or NSTEMI (300)	Alirocumab 150 mg every 2 wk (148) vs placebo (152)	NIRS-IVUS and OCT	12	Alirocumab vs placebo. Absolute change from baseline: −122.5 (95% CI: −128.8 to −116.3) vs −64.8 (95% CI: −71.5 to −58.0) ($P < 0.001$)	Alirocumab vs placebo. Change in percent atheroma volume: −2.13% (95% CI: −2.5% to −1.73%) vs −0.92% (95% CI: −1.28% to −0.56%) ($P < 0.001$) Change in maxLCBI$_{4mm}$: −79.42 (95% CI: −100.3 to −58.48) vs −37.60 (95% CI: −57.4 to −17.80) ($P = 0.006$) Change in minimal fibrous cap thickness: 62.67 μm (95% CI: 48.8 to 76.50 μm) vs 33.19 μm (95% CI: 22.22 to 44.16 μm) ($P = 0.001$)	Alirocumab vs placebo. All-cause death: 2 (1.4%) vs 1 (0.7%) Cardiac death: 2 (1.4%) vs 0 MI: 2 (1.4%) vs 3 (2.0%) Ischemia-driven revascularization: 12 (8.2%) vs 28 (18.5%)

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ezetimibe, to proprotein convertase subtilisin/kexin type-9 (PCSK-9) inhibitors and icosapent ethyl, to diverse anti-inflammatory therapies, a variety of pharmacologic treatments for secondary prevention of cardiovascular disease have led to a reduction in ischemic cardiovascular events in patients with established CAD.[40]

Lipid-lowering therapy. According to contemporary clinical guidelines of stable CAD or ACS, patients with established CAD are regarded as being at very high risk for cardiovascular events.[17,18,41] Therefore, high-dose statin therapy must be considered to address low-density lipoprotein cholesterol (LDL-C) levels. If LDL-C cannot be controlled on a maximum tolerated dose of statin, ezetimibe and PCSK-9 inhibitors should be added sequentially.[17,18] Although there are no specific recommendations to treat vulnerable plaque detected by intracoronary imaging

TABLE 2 Continued

Study (Year)	Cohort (N)	Comparison (N)	Evaluation Method	Therapy Duration (mo)	Change in LDL-C Levels (mg/dL)	Change in Plaque Burden, Fibrous Cap Thickness (mm), Lipid Arc (°), or MaxLCBI$_{4mm}$	Comparison in Clinical Outcomes
Stable CAD							
ASTEROID (2006)[48]	Patients with stable or unstable ischemic chest pain (507)	Rosuvastatin 40 mg/d	IVUS	24	Baseline 130.4 ± 34.3; follow-up 133.8 ± 25.4; percent change −53.2% (95% CI: −55.6% to −50.9%)	Change in percent atheroma volume: −0.98% ± 3.15% ($P < 0.001$ from baseline)	Death: 0.8% MI: 2.0% Stroke: 0.6%
COSMOS (2009)[49]	Stable CAD (214)	Rosuvastatin titrated up to a maximum 20 mg/d	IVUS	18	Baseline 140.2 ± 31.5; follow-up 82.9 ± 18.7; percent change −38.6% ± 16.9% ($P < 0.0001$)	Change in plaque volume: −5.1% ± 14.1% (95% CI: −7.6% to −2.6%) ($P < 0.0001$ from baseline)	No death, MI, and stroke in either group.
YELLOW (2013)[50]	Stable CAD (87)	Rosuvastatin 40 mg/d (Intensive) (44) vs standard-of-care lipid-lowering therapy (43)	NIRS-IVUS	1.5	Intensive vs standard Baseline 79.1 ± 25.3; follow-up 58.4 ± 26.3 vs baseline 82.8 ± 26.9; follow-up 81.9 ± 27.9 ($P < 0.001$ for follow-up values)	Intensive vs standard Change in maxLCBI$_{4mm}$: −149.1 (95% CI: −210.9 to −42.9) vs 2.4 (95% CI: −36.1 to −44.7) ($P = 0.01$) Percent change in maxLCBI$_{4mm}$: −32.2 (95% CI: −40.4 to −12.4) vs −0.6 (95% CI: −22.0 to 12.4) ($P = 0.02$) Change in plaque burden: baseline 75.9%; follow-up 75.3% vs baseline 75.6%; follow-up 74.9% ($P = 0.83$ for follow-up values)	Intensive vs standard No death in either group. Unplanned revascularization: 3 (6.8%) vs 2 (4.7%)
REVERSAL (2004)[51]	Stable CAD (654)	Atorvastatin 80 mg/d (intensive) (327) vs pravastatin (moderate) (327)	IVUS	18	Intensive vs moderate. Baseline 150.2 ± 27.9; follow-up 78.9 ± 30.2; percent change from baseline −46.3% vs Baseline 150.2 ± 25.9; follow-up 110.4 ± 25.8; percent change from baseline −25.2% ($P < 0.001$)	Intensive vs moderate. Change in percent atheroma volume: 0.6% ± 5.1% vs 1.9% ± 4.9% ($P < 0.001$)	Intensive vs moderate. Death: 1 (0.3%) vs 1 (0.3%) MI: 7 (2.1%) vs 4 (1.2%) Stroke: 1 (0.3%) vs 1 (0.3%)
SATURN (2011)[52]	Stable CAD (1039)	Atorvastatin 80 mg/d (519) vs Rosuvastatin 40 mg/d (520)	IVUS	24	Atorvastatin vs rosuvastatin. Baseline 119.9 ± 28.9; follow-up 70.2 ± 1.0 vs baseline 120.0 ± 27.3; follow-up 62.6 ± 1.0 ($P < 0.001$ for follow-up values)	Atorvastatin vs rosuvastatin. Change in percent atheroma volume: −0.99% (95% CI: −1.19% to −0.63%) vs −1.22% (95% CI: −1.52% to −0.90%) ($P = 0.17$)	Atorvastatin vs rosuvastatin. CV death: 2 (0.3%) vs 2 (0.3%) Nonfatal MI: 11 (1.6%) vs 11 (1.6%) Hospitalization for unstable angina: 13 (1.9%) vs 16 (2.3%) Arterial revascularization: 41 (6.0%) vs 42 (6.1%)
HEAVEN (2012)[58]	Stable CAD (89)	Atorvastatin 80 mg/d plus ezetimibe 10 mg/d (aggressive) (42) vs standard therapy (47)	VH-IVUS	12	Aggressive vs standard. Baseline 3.1 ± 1.3 mmol/L; follow-up 2.0 ± 0.8 mmol/L; percent change from baseline −28.6 ± 33.8% vs Baseline 2.7 ± 0.8 mmol/L; follow-up 2.6 ± 0.8 mmol/L; percent change from baseline −1.9% ± 29.8% ($P = 0.0002$)	Aggressive vs standard. Change in percent atheroma volume: −0.4% ± 2.9% vs 1.4% ± 4.2% ($P = 0.014$) Change in fibrous component: −0.4% ± 5.5% vs −1.3% ± 8.9% ($P = 0.56$) Change in fibrofatty component: −1.8% ± 8.0% vs −3.3% ± 11.1% ($P = 0.47$) Change in necrotic core: 1.5% ± 6.1% vs 3.4% ± 7.2% ($P = 0.18$) Change in calcification: 1.0% ± 5.9% vs 2.6% ± 5.0% ($P = 0.18$)	-

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modalities, guideline-directed lipid-lowering therapy is a cornerstone of secondary prevention in patients with documented CAD. Several RCTs and observational studies have demonstrated the clinical effectiveness of lipid-lowering therapy for patients with documented CAD in whom vulnerable plaques were evaluated with serial intracoronary imaging at baseline and follow-up. Table 2 summarizes the key

TABLE 2 Continued

Study (Year)	Cohort (N)	Comparison (N)	Evaluation Method	Therapy Duration (mo)	Change in LDL-C Levels (mg/dL)	Change in Plaque Burden, Fibrous Cap Thickness (mm), Lipid Arc (°), or MaxLCBI$_{4mm}$	Comparison in Clinical Outcomes
ZIPANGU (2017)[59]	Stable CAD (131)	Atorvastatin 10-20 mg/d plus ezetimibe 10 md/d (combination) (65) vs atorvastatin 10-20 mg/d (monotherapy) (66)	IVUS	9	Combination vs monotherapy. Baseline 101 ± 27; follow-up 61 ± 17 vs baseline 101 ± 27; follow-up 75 ± 16 ($P < 0.001$ for follow-up values)	Combination vs monotherapy. Change in plaque volume: Baseline 50.0% ± 9.8%; follow-up 49.3% ± 9.8% ($P = 0.03$) vs baseline 48.5% ± 10.2%; follow-up 48.2% ± 10.4% ($P = 0.4$) Change in yellow color grade from baseline: −0.4 ± 1.4 vs −0.4 ± 1.4 ($P = 0.6$)	-
GLAGOV (2016)[66]	Stable CAD (968)	Evolocumab 420 mg monthly (484) vs placebo (484)	IVUS	18	Evolocumab vs placebo. Absolute change from baseline: −56.3 (95% CI: −59.4 to −53.1) vs 0.2 (95% CI: −2.9 to 3.4) ($P < 0.001$)	Evolocumab vs placebo. Change in precent atheroma volume: −0.95% (95% CI: −1.33% to 0.58%) vs 0.05% (−0.32% to 0.42%) ($P < 0.001$) Change in total atheroma volume: −5.80 mm^3 (95% CI: −8.19 to 3.41 mm^3) vs −0.91 mm^3 (−3.29 to 1.47 mm^3) ($P < 0.001$)	Evolocumab vs placebo. Death: 3 (0.6%) vs 4 (0.8%) Nonfatal MI: 10 (2.1%) vs 14 (2.9%) Hospitalization for unstable angina: 3 (0.6%) vs 4 (0.8%) Coronary revascularization: 50 (10.3%) vs 66 (13.6%)
Hirai et al (2020)[67]	Stable CAD (98)	Evolocumab 140 mg every 2 wk plus statin (82) vs statin only (16)	coronary CTA	6	Evolocumab plus statin vs statin only. Baseline 70.4 ± 21.5; follow-up 19.3 ± 16.0 ($P < 0.001$) vs Baseline 80.5 ± 28.4; follow-up 68.6 ± 20.5 ($P < 0.09$)	Evolocumab plus statin vs statin only. The minimum CT density (39.1 ± 8.1 HU vs 84.9 ± 31.4 HU; $P < 0.001$) The remodeling index (1.29 ± 0.11 vs 1.19 ± 0.10; $P < 0.001$) Percent stenosis (27.0% ± 10.4% vs 21.2% ± 9.8%; $P < 0.001$)	

IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein cholesterol; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TL = target lesion; TLR = target lesion revascularization; TV = target vessel; TVR = target vessel revascularization; other abbreviations as in Table 1.

clinical studies of lipid-lowering therapy for patients with vulnerable plaque.

Statins. Vulnerable plaques are more likely to be present in vulnerable patients such as those presenting with ACS.[5,6] Statins have documented benefit on vulnerable plaque regression and improve clinical outcomes in patients with ACS. The ESTABLISH (Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Serial Volumetric Intravascular Ultrasound Analysis During Half a Year After Coronary Event) study,[42] in which 70 patients with ACS underwent PCI and were randomized to atorvastatin at 20 mg daily or the control group, demonstrated that 20 mg of atorvastatin significant reduced IVUS-measured plaque volume compared with the control group (13.1% vs 8.7%; $P < 0.001$) after 6 months. In the IBIS-4 (Integrated Biomarkers and Imaging Study),[43] 103 patients with ST-segment elevation myocardial infarction (STEMI) who were treated with high-dose rosuvastatin (40 mg daily) and underwent IVUS and radiofrequency ultrasound of noninfarct-related arteries. After 13 months, the serial IVUS revealed that the percent atheroma volume of nonculprit-lesions decreased by −0.9% (95% CI: −1.56 to −0.25) without changes in necrotic core and radiofrequency IVUS defined TCFA. The JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study[44] examined the effects of pitavastatin and atorvastatin in coronary plaque regression in nonculprit vessels in those with ACS; both statins effectively reduced IVUS-measured plaque volume (−16.9% in pitavastatin and −18.1% in atorvastatin). In the STABLE (Statin and Atheroma Vulnerability Evaluation) trial,[45] 312 patients with stable CAD or ACS who had at least 1 nonculprit VH-IVUS-defined TCFA lesion, were randomly assigned to low-dose (10-mg) or high-dose (40-mg) rosuvastatin. During follow-up, the use of rosuvastatin significantly reduce the necrotic core and plaque volume and decreased TCFA, but there were no significant differences between low-dose vs high-dose rosuvastatin. The EASY-FIT (Effect of AtorvaStatin therapY on Fibrous cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography) study[46] compared the change of fibrous cap thickness in comparison with 20 mg vs 5 mg

atorvastatin in patients with unstable angina; fibrous cap thickness was significantly increased and the lipid arc and macrophage content were decreased with high-dose atorvastatin. In the ESCORT (Effect of PitavaStatin on Coronary Fibrous-cap Thickness-Assessment by Fourier-Domain Optical CoheRence Tomography) study,[47] OCT-measured fibrous cap thickness was more increased in the early pitavastatin group than in the late pitavastatin group.

Like ACS patients, patients with stable CAD could also have atherosclerotic plaques with vulnerable characteristics. Several imaging studies have been conducted in patients with stable CAD. In the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial,[48] 507 patients who were presented with stable ischemic chest pain and had mild-to-intermediate (20%-50%) CAD were treated with 40 mg of rosuvastatin. IVUS-measured precent atheroma volume was significantly reduced during 2 years. The COSMOS (The Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) study,[49] in which 214 patients with stable CAD were treated with rosuvastatin for 76 weeks, showed similar outcomes as the ASTEROID trial. In the YELLOW (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy) trial,[50] 87 patients with chronic stable angina and severe obstructive CAD (angiographic DS >70% and FFR ≤0.8) were randomly assigned to intensive treatment (rosuvastatin 40 mg daily) or a standard-of-care lipid-lowering therapy. The median percent reduction in $\text{maxLCBI}_{4\text{mm}}$ was greater in the intensive group compared with the standard-care group after 7 weeks (32.2% vs 0.6%). In the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial,[51] 654 patients with stable CAD (angiographic DS 20%-50%) were randomly assigned to receive a moderate lipid-lowering regimen of 40 mg of pravastatin or an intensive lipid-lowering regimen of 80 mg of atorvastatin. Patients in the atorvastatin group had reduced progression of coronary atherosclerosis compared with the pravastatin group. In the SATURN (The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) trial,[52] investigators performed serial IVUS in 1,039 patients with stable CAD (angiographic DS 20%-50%) at baseline and after 104 weeks of treatment with either atorvastatin at 80 mg daily or rosuvastatin 40 mg daily. There was no between-group difference in significant changes of the percent atheroma volume.

Ezetimibe. Several trials have evaluated the effects of adding ezetimibe to statin therapy on coronary plaques assessed by intracoronary imaging. The PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial[53] evaluated the effects of ezetimibe added to atorvastatin on coronary atheroma volume measured by IVUS in 202 patients with stable CAD or ACS who underwent PCI. At 9 to 12 months, the percent atheroma volume was significantly reduced in the combination therapy compared with the atorvastatin monotherapy (−1.4% vs −0.3%, respectively; $P = 0.001$). Similarly, in the ZEUS (eZEtimibe Ultrasound Study) trial,[54] including 95 ACS patients, and the OCTIVUS (Ezetimibe in Addition to Atorvastatin Therapy on the Plaque Composition in Patients with Acute Myocardial Infarction) trial,[55] including 87 STEMI patients, ezetimibe combined with statin therapy showed more plaque regression compared with statin therapy alone. By contrast, in another study of 128 patients with ACS comparing ezetimibe plus pitavastatin and pitavastatin alone,[56] there were no between-group differences in the percent changes in plaque volume and lipid plaque volume.

The additive effect of ezetimibe on coronary plaque regression was also tested in patients with stable CAD. In a study including 51 patients with stable CAD,[57] IVUS-measured plaque volume at nonculprit target lesions was significantly lower in the combination therapy group (10 mg of ezetimibe plus 5 mg of rosuvastatin) compared with the monotherapy group (5 mg of rosuvastatin) (−13.2% vs −3.1%, respectively). In the HEAVEN (Virtual Histology Evaluation of Atherosclerosis Regression During Atorvastatin and Ezetimibe Administration) study,[58] 89 patients with stable angina who had mild-to-intermediate narrowing of angiographic DS 20% to 50% were randomly assigned to receive either combination therapy (10 mg of ezetimibe plus 80 mg of atorvastatin) or standard therapy (10 mg of atorvastatin). After 12 months, the IVUS-measured plaque volume was significantly decreased in the combination group (−0.4% vs +1.4%, respectively), but there was no significant between-group difference in plaque composition measured by VH-IVUS. Similarly, the ZIPANGU (Ezetimibe Clinical Investigation for Regression of Intracoronary Plaque Evaluated by Angioscopy and Ultrasound) study,[59] including 131 patients with stable CAD, showed a significant reduction in plaque volume with the combination therapy (ezetimibe at 10 mg daily and atorvastatin at 10-20 mg) compared with statin monotherapy (atorvastatin at 10-20 mg).

PCSK-9 inhibitors. PCSK9 inhibitors added to intensive statin therapy incrementally reduced cardiovascular outcomes.[60-62] The effect of PCSK9 inhibitors on plaque regression has been evaluated in several studies. In the ODYSSEY J-IVUS (Evaluation of Effect of Alirocumab on Coronary Atheroma Volume in Japanese Patients Hospitalized for Acute Coronary Syndrome with Hypercholesterolemia) trial,[63] 206 patients with ACS were randomly assigned to receive 75 mg of alirocumab every 2 weeks with statin therapy or statin therapy alone. After 36 weeks, the percent change in total atheroma volume was not significantly different between the 2 groups (−4.8% in the alirocumab group vs −3.1% in the statin group, respectively; $P = 0.23$) despite a significant reduction in LDL-C levels in the alirocumab group (63.9% vs 13.4% from baseline, respectively). The HUYGENS (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) trial assessed whether PCSK9 inhibition by evolocumab in addition to high-intensity statin therapy favorably modified the coronary plaque phenotype,[64] in which 161 patients with non-STEMI underwent OCT for nonculprit lesions (angiographic DS 20%-50%). At 50 weeks, a greater increase of minimum fibrous cap thickness and a decrease of maximum lipid arc and macrophage index were noted in the evolocumab group. The PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction) trial evaluated the effect of early administration of alirocumab on coronary atherosclerotic plaque using multimodality imaging modalities (IVUS, NIRS, and OCT),[65] in which 300 patients with acute MI had imaging evaluation of nonculprit atherosclerosis (angiographic DS 20%-50%). At 52 weeks, alirocumab was associated with a reduction of percent atheroma volume and $\text{maxLCBI}_{4\text{mm}}$ and an increase of minimal fibrous thickness. In the GLAGOV (Global Assessment of Plaque Regression with PCSK9 Antibody as Measured by Intravascular Ultrasound) trial,[66] in which 968 patients with stable CAD and angiographic DS 20% to 50% were randomized to receive monthly evolocumab or placebo for 76 weeks in addition to statin. The evolocumab group demonstrated a reduction of percent and total atheroma volume compared with the placebo group. A small coronary CTA study of 98 patients with stable CAD evaluating the effect of evolocumab on vulnerable coronary plaques showed that evolocumab stabilized vulnerable coronary plaques and reduced their size.[67]

Other potential medical drugs. Omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid, have anti-inflammatory and antioxidative properties and promote lipoprotein metabolism.[68,69] In the CHERRY (Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography) study including 193 patients with stable CAD and ACS,[70] the total atheroma volume was significantly reduced in the EPA group (EPA at 1,800 mg/d and pitavastatin at 4 mg/d) compared with the pitavastatin group. In the HEARTS (Slowing HEART Disease with Lifestyle and Omega-3 Fatty Acids) trial, which randomized 258 patients with stable CAD to an omega-3 group (1.86 g of EPA and 1.5 g of docosahexaenoic acid daily) or no omega-3 group for 30 months, there were no differences in the plaque volume as measured by coronary CTA or in adverse clinical events.[71] The EVAPORATE (Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy) trial randomized 80 patients with stable CAD to receive either icosapent ethyl (a purified EPA ethyl ester) at 4 g/d or a mineral oil placebo for 18 months.[72] The coronary CTA-detected total, fibrofatty, fibrous, and low-attenuation plaque volume at 18 months was significantly reduced in the icosapent ethyl group. In a study including 210 patients with ACS, serial coronary CTA showed that addition of high-dose EPA (1,800 mg/d) to statin therapy was associated with a lower rate of plaque progression.[73] Small OCT studies showed that EPA added to statin increased fibrous cap thickness compared with statin alone.[74,75]

Inflammation plays an important role in the progression of CAD; the accumulation of cholesterol within the vessel wall induces inflammation, which makes coronary plaques more vulnerable.[76,77] Colchicine, an anti-inflammatory drug, has demonstrated its effect of lowering the risk of cardiovascular events in RCTs and has now been recommended in clinical guideless (Class IIb).[78-80] In a prospective observational coronary CTA study,[81] in which 80 patients with recent ACS received either colchicine (0.5 mg/d) plus OMT or OMT alone, colchicine significantly reduced low-attenuation plaque volume (−40.9% vs −17.0%, respectively) and high-sensitivity C-reactive protein (−37.3% vs −14.6%, respectively) compared with OMT alone at 1 year.

II. INVASIVE STRATEGY OF LOCAL PREVENTIVE THERAPY. The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial and recent meta-analyses have shown that revascularization on top of OMT in patients with stable CAD reduces spontaneous MI and hospitalization for unstable angina without

TABLE 3 Summary of Completed and Ongoing Clinical Trials of the Local Preventive Therapy for Vulnerable Plaques

Study (Year)	Status	Objective	Study Design	N	Population and Lesion Characteristics	Intervention	Primary Outcomes	Clinical Trial Registry Number
PROSPECT-ABSORB (2020)	Completed	To examine the outcomes of PCI of nonflow-limiting vulnerable plaques	Randomized trial	182	Patients with acute MI who underwent successful PCI of all flow-limiting coronary lesions. Patients with an angiographically nonobstructive stenosis with IVUS plaque burden >65% were randomized.	BVS plus GDMT vs GDMT alone	IVUS-derived MLA at 25-mo follow-up	NCT02171065
PECTUS (2020)	Prematurely halted	To assess the safety and efficacy of pre-emptive treatment of OCT-derived vulnerable, nonflow-limiting, nonculprit lesions	Randomized trial	34	Patients presenting with MI, nonculprit lesions with a FFR >0.8 were imaged with OCT and then vulnerable plaques were randomized.	PCI with BVS plus OMT vs OMT alone	A composite of all-cause mortality, nonfatal MI, and unplanned revascularization at 1 y	
PREVENT	Ongoing	To examine the role of preventive PCI with BVS (early period) or everolimus-eluting stents (middle and late period) plus OMT on functionally insignificant (FFR >0.80) vulnerable coronary plaque	Randomized trial	1,608	Patients with at least 1 significant stenosis (diameter stenosis >50%) with FFR >0.80 and meeting 2 of the following criteria: 1. MLA <4 mm^2 2. Plaque burden >70% 3. $MaxLCBI_{4mm}$ >315 4. TCFA	PCI with BVS (early period) or everolimus-eluting stents (middle and late period) plus OMT vs OMT alone	Target vessel failure (composite of cardiac death, target-vessel MI, ischemia-driven TVR, or hospitalization for unstable or progressive angina) at 2 y	NCT02316886
COMBINE INTERVENE	Ongoing	To investigate whether a PCI revascularization strategy based on combined FFR and OCT assessment is superior to a PCI revascularization strategy based on FFR alone	Randomized trial	1,222	Patients undergoing PCI and meeting following angiographic criteria: presence of ≥2 de novo target lesions (diameter stenosis ≥50% on visual estimation) located in 2 different native coronary arteries feasible for treatment with PCI.	PCI based on FFR and OCT assessment (All FFR ≤0.75 and vulnerable plaque including TCFA, ruptured plaque, MLA <2.5 mm^2 will be treated) vs PCI based on FFR assessment (all lesions with FFR ≤0.80 will be treated)	A composite of cardiac death, any MI, or any clinically driven revascularization at 24 mo	NCT05333068
FAVOR V AMI[a]	Ongoing	To compare long-term clinical outcomes of the functional and angiography-derived strain integration technique (next-generation QFR [μQFR] and radial wall strain [RWS]) guided PCI with standard treatment strategy	Randomized trial	5,000	After successful PCI of the culprit lesion for STEMI, all noninfarct related arteries with diameter stenosis 50%-90% and reference vessel diameter ≥2.5 mm were evaluated with next-generation μQFR and RWS in the experimental arm.	PCI based on physiology (μQFR) and vulnerable plaque characteristics (RWS) vs PCI based in visual estimation (diameter stenosis ≥ 70%) or physiology (FFR ≤0.80 or iFR ≤0.89)	A composite of all-cause death, MI, or ischemia-driven revascularization	NCT05669222
VULNERABLE	Ongoing	To compare preventive PCI plus OMT strategy vs OMT alone for treatment of nonfunctionally significant nonculprit lesions with vulnerable plaque on OCT	Randomized trial	600	After successful PCI of the culprit lesion for STEMI, intermediate lesions (diameter stenosis 40%-69%) are investigated with FFR. Lesions with FFR >0.80 are then investigated with OCT. Patients with vulnerable plaques on OCT are included and randomized.	PCI plus OMT vs OMT	Target vessel failure (composite of cardiovascular death, target-vessel MI, and TVR) at 4 y	NCT05599061

Continued on the next page

TABLE 3 Continued

Study (Year)	Status	Objective	Study Design	N	Population and Lesion Characteristics	Intervention	Primary Outcomes	Clinical Trial Registry Number
INTERCLIMA	Ongoing	To assess the clinical effectiveness of an OCT-based strategy to guide revascularization in nonculprit intermediate coronary stenosis	Randomized trial	1,420	In ACS patients undergoing coronary angiography, intermediate lesions (diameter stenosis 40%-70% on QCA) are randomized to OCT-based treatment or physiology-based treatment.	OCT-guided PCI (FCT <75 μm plus at least 2 of 3 other OCT criteria of plaque vulnerability (MLA <3.5 mm^2, lipid arch with circumferential extension >180°, and the presence of macrophages) vs physiology-guided PCI (an iFR or RFR ≤0.89 or an FFR ≤0.80)	A composite of cardiac death and nonfatal spontaneous target-vessel MI at 2 y	NCT05027984

[a]FAVOR V AMI is a mixed trial of treatment dictated by abnormal physiology (quantitative flow ratio [μQFR]) or vulnerable plaque characteristics (radial wall strain [RWS]) in the experimental arm.

BVS = bioabsorbable vascular scaffold; FCT = fibrous cap thickness; FFR = fractional flow reserve; GDMT = guideline-directed medical therapy; iFR = instantaneous wave-free ratio; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RFR = resting full-cycle ratio; other abbreviations as in Tables 1 and 2.

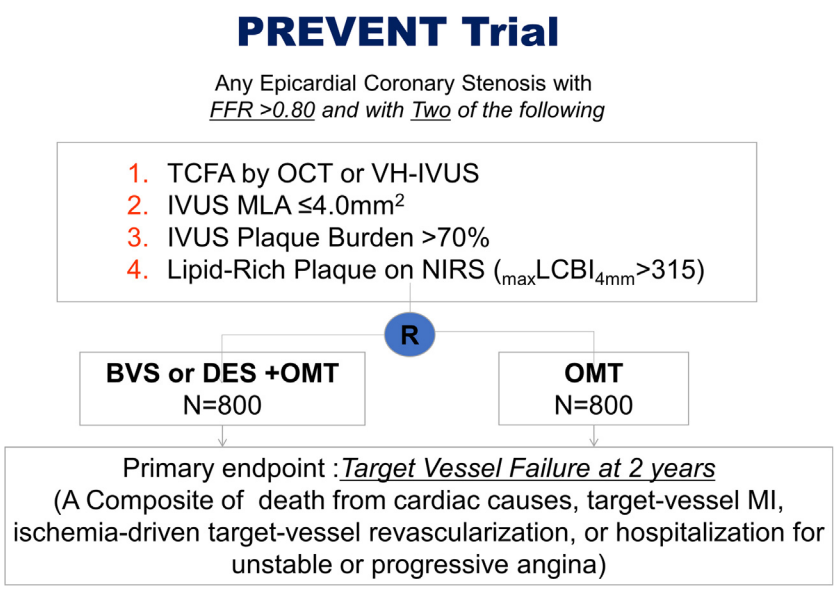
differences of all-cause mortality.[82-84] Although PCI shows no evidence of an effect on hard clinical outcomes for patients with stable CAD, PCI prevents death, cardiac death, and MI in patients with unstable CAD.[83] Given that patients with ACS have a residual risk for recurrent cardiovascular events[85] and vulnerable plaques are often present in untreated nonculprit lesions,[5,86,87] it would be theoretically possible that local preventive revascularization on vulnerable plaques might reduce adverse cardiovascular outcomes.[83] In this clinical context, the result of the OCT-substudy of the COMPLETE (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI) trial,[87] which observed 56% of all TCFA occurred in untreated angiographically nonobstructive nonculprit lesions, suggests that the future event risk of such vulnerable plaque could be clinically relevant and, thus, reinforces that further additional therapy targeting vulnerable plaque could reduce adverse cardiovascular events. However, until recently, there have been no recommendations regarding revascularization of nonischemia-producing vulnerable plaque, and there is also limited clinical evidence on whether local prophylactic revascularization of the vulnerable plaque might improve patient-oriented clinical outcomes.[17,18,23]

Prior imaging studies showed important findings providing the theoretical concept of preventive PCI; PCI with metallic stents or bioresorbable vascular scaffold (BVS) on coronary vulnerable plaques results in thick-cap fibroatheroma transformations, wall shear stress normalization, and enlargement of coronary lumen.[21,88,89] The completed and ongoing trials of the local preventive therapy for vulnerable plaques are summarized in Table 3. The PROSPECT-ABSORB trial evaluated whether prophylactic PCI with BVS of high-risk vulnerable plaque is safe and effective.[23] A total of 182 patients with acute MI who underwent successful PCI of all lesions responsible for the ACS and had at least 1 lesion with an angiographic DS <70% (with negative FFR or instantaneous wave-free ratio, but with plaque volume by IVUS of ≥65%) were randomly assigned to BVS plus GDMT or GDMT alone. At 25 months, the MLA was significantly larger (6.9 mm^2 vs 3.0 mm^2, respectively; $P < 0.0001$) and the maximum lipid content (max $LCBI_{4mm}$) was significantly lower (median 6.2% vs 26.9%, respectively; $P < 0.0001$) in the BVS group than in the GDMT-only group. The incidence of target-lesion failure (composite of cardiac death, target vessel-related MI, or clinically driven target lesion revascularization) at 2 years were similar in both groups (4.3% in BVS groups vs 4.5% in GDMT only group). Another PECTUS (Pre-Emptive OCT-Guided Angioplasty of Vulnerable Intermediate Coronary Lesions) trial,[22] which was halted prematurely because of the removal of BVS from the market, assessed the safety and efficacy of preemptive OCT-guided PCI for nonflow-limiting vulnerable plaques. The study involved 34 patients randomized to receive either BVS plus OMT or OMT only. During 2 years of follow-up, MACE was reported in 3 patients (18.8%) in the BVS group and 1 patient (6.3%) in the OMT group, but target lesion failure did not occur in the BVS group and was reported in only 1 patient in the OMT group.

Unfortunately, prior available studies on the local therapy of vulnerable plaques were not powered for

JACC: ASIA, VOL. 4, NO. 6, 2024
JUNE 2024:425–443

FIGURE 1 The Design of the PREVENT Trial

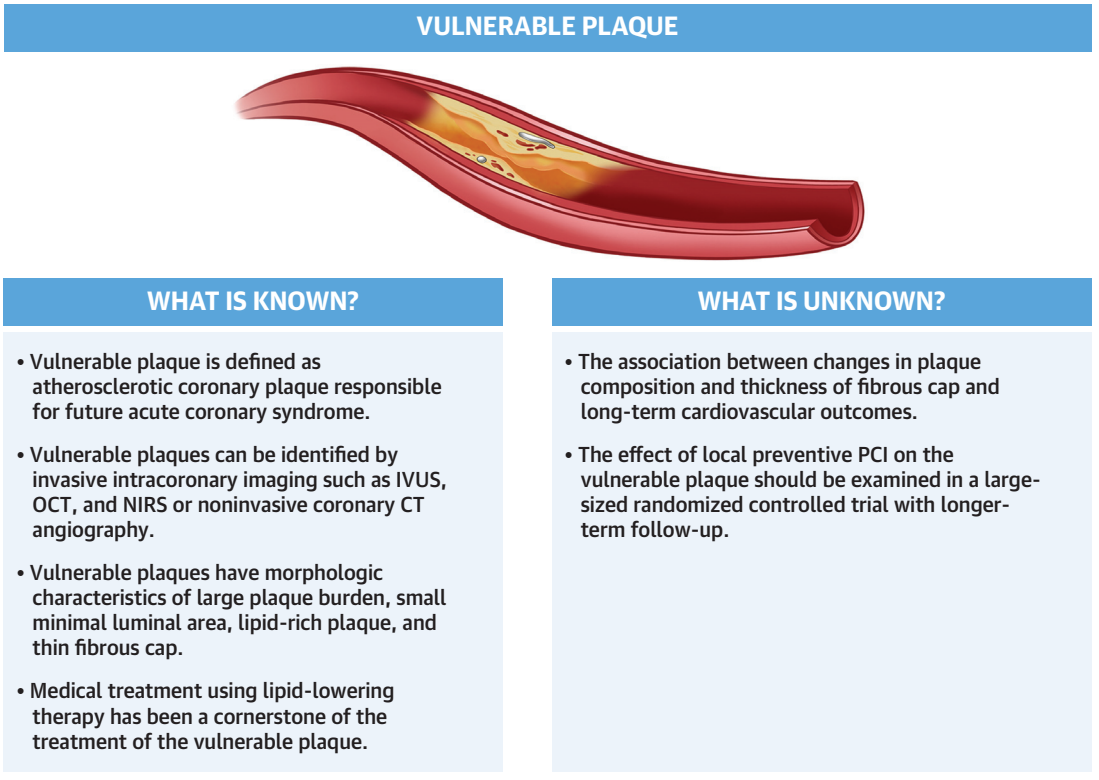


The design of the PREVENT (Preventive PCI or Medical Therapy Alone for Vulnerable Atherosclerotic Coronary Plaque) trial is shown. BVS = bioresorbable vascular scaffold; DES = drug-eluting stent(s); FFR = fractional flow reserve; IVUS = intravascular ultrasound; LCBI = lipid core burden index; MI = myocardial infarction; NIRS = near infrared spectroscopy; OCT = optical coherence tomography; OMT = optimal medical therapy; TCFA = thin cap fibroatheroma; VH-IVUS = virtual histology intravascular ultrasound.

relevant clinical outcomes. Therefore, large-scale, appropriately powered RCTs have been demanded to evaluate the effects of local prophylactic PCI on vulnerable plaque. The PREVENT (Preventive PCI or Medical Therapy Alone for Vulnerable Atherosclerotic Coronary Plaque; NCT02316886) aims to determine whether preventive PCI with BVS (early period) or everolimus-eluting stents (middle and late periods) plus OMT on functionally insignificant (FFR >0.80) vulnerable plaque would reduce adverse cardiovascular outcomes at 2 years compared with OMT alone. Eligible patients should have at least 1 angiographically significant stenosis (DS >50%) without functional significance (fractional flow reserve >0.80), for which intracoronary imaging was performed for assessment of plaque characteristics. Intracoronary imaging was used at operator discretion with grayscale IVUS, radiofrequency IVUS, the combination of gray-scale IVUS and NIRS, or OCT. Target lesions should have at least 2 of the following intracoronary imaging criteria for vulnerable plaque: 1) MLA <4.0 by mm^2 by IVUS or OCT; 2) plaque burden >70% by IVUS; 3) $maxLCBI_{4mm}$ >315 by NIRS; and 4) TCFA as determined by radiofrequency IVUS or OCT. Enrolled patients are randomly assigned in a 1:1 ratio to either a preventive PCI with BVS or everolimus-eluting stent or an OMT alone. The primary endpoint is a target-vessel failure, which is defined as a composite of death from cardiac causes, target-vessel myocardial infarction, ischemic-driven target-vessel revascularization, and hospitalization for unstable or progressive angina, at 2 years after randomization. In both groups, OMT consisted of lifestyle modification and intensive pharmacologic interventions, based on contemporary guideline-directed medical therapies. If guidelines are updated or new pharmacologic agents are approved, these amendments were considered for incorporation into this trial. High-dose statin therapy was recommended to achieve targeted LDL-C levels. Lifestyle modifications and risk factor management included smoking cessation, optimization of nutrition, physical activity, adherence to prescribed medications, and control of diabetes and hypertension. Thus far, more than 1,600 patients have been enrolled, and the results will be available in early 2024 (**Figure 1**).[90]

Besides the implantation of metallic stents or BVS, alternative focal therapies for the treatment of vulnerable plaques have been investigated including drug-coated balloons, cryotherapy, and photodynamic therapy.[91-93] The DEBuT-LRP (Intravascular Identification and Drug-Eluting Balloon Treatment of

CENTRAL ILLUSTRATION **Summary for Known Knowledge and Unknown Issues of Vulnerable Plaques**



Known knowledge and unknown issues on the vulnerable plaque are shown. IVUS = intravascular ultrasound; NIRS = near infrared spectroscopy; OCT = optical coherence tomography; PCI = percutaneous coronary intervention.

Vulnerable Lipid-Rich Plaques; NCT04765956) enrolled 45 participants to evaluate the safety and efficacy of a drug-coated balloon to treat lipid-rich plaque identified by NIRS-IVUS.[91] The study will provide evidence on whether drug-coated balloon could be used safely and effectively to treat vulnerable plaque.

However, several issues must be still addressed in prophylactic PCI of vulnerable plaques; PCI for lipid-rich vulnerable plaque might result in an increase of periprocedural MI because of distal embolization of the lipid-rich plaque and late restenosis or stent thrombosis. The CANARY (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow) trial[94] examined whether NIRS-identified pre-PCI plaque characterization is associated with an increased risk of periprocedural MI. Periprocedural MI developed in 24.7% of the patients, and the $\text{maxLCBI}_{4\text{mm}}$ was higher in patients with periprocedural MI than those without (481.5 vs 371.5, respectively). The trial may emphasize the safety concern of prophylactic PCI for the vulnerable, which could be associated with periprocedural MI and other procedural complications. In addition, local preventive PCI requires invasive coronary angiography and intracoronary imaging for all nonobstructive nonculprit lesions. This strategy may not be practical or feasible in routine clinical practice.

In addition, from a clinical viewpoint, the implications of the relative and absolute patient- and lesion-level risks of vulnerable plaques should be considered. Several prospective analyses of vulnerable plaques have a poor positive predictive value for plaque-specific clinical events.[5,95,96] In PROSPECT,

596 TCFA were identified using IVUS, but only 26 (4.3%) MACE events were directly related to TFCA during the 3 years.[5] In SCOT-HEART, CT-detected high-risk coronary plaques were observed in 608 patients, of whom only 25 experienced subsequent MI or cardiac death (4.1%) during 5 years.[95] In PROMIS (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), high-risk plaques were detected on coronary CTA in 505 patients with nonobstructive CAD, of whom only 24 (4.8%) experienced MACE during a median 2-year follow-up.[96] Thus, given a lower absolute risk associated with vulnerable plaque-related coronary events, concern has been expressed that these event rates might be too low to improve by focal therapy. Finally, prospective data from well-designed and adequately powered RCTs are required to prove the safety and effectiveness of focal therapy of vulnerable plaques.

HIGHLIGHTS

- With advancements intracoronary imaging, vulnerable coronary plaques responsible for future cardiovascular events can be identified.
- Considering that recurrent adverse cardiovascular events still occur despite OMT including lipid-lowering therapy, there are unmet needs for further management of vulnerable plaques.
- As a local preventive therapy, preventive PCI for vulnerable plaque could be an option, and the PREVENT trial will provide evidence on the optimal treatment for vulnerable plaque beyond medical treatments.

FUTURE PERSPECTIVES AND DIRECTION

The contemporary practice guidelines recommend PCI only for ischemia-inducing significant CAD.[19,97] However, long-term follow-up studies have shown that adverse cardiovascular events frequently occur in nonflow-limiting (FFR negative) coronary lesions containing vulnerable plaques.[7,98] Given that vulnerable plaque identified by diverse intracoronary imaging is prone to future unexpected coronary events despite guideline-directed OMT for secondary prevention, more clinical evidence on optimal management of nonflow-limiting vulnerable plaque is needed. To date, several studies have explored percutaneous approaches to seal and stabilize focal areas of vulnerable plaques. However, most available studies still suffer from the limited study power, duration of follow-up, and inconclusive data. Therefore, the PREVENT trial will provide evidence for the treatment of nonflow-limiting vulnerable plaque, specifically on whether local preventive PCI plus OMT would be better compared with OMT alone.[90] Key findings of the PREVENT trial will provide novel perspective, suggesting that preventive PCI may modify the long-term prognosis of nonflow-limiting, high-risk focal vulnerable plaques, which are not sufficiently managed with OMT alone.

In the practical viewpoint, the clinical application of PCI on vulnerable plaque is more clearly defined. This approach requires invasive imaging and is, therefore, likely to be applicable mainly to patients already referred for invasive angiography. The practicality of this invasive approach is still uncertain, and whether most patients require 3-vessel invasive imaging or a more targeted imaging approach has not been determined. Furthermore, systematic pharmacologic therapies have been used in large segments of patients with documented CAD, with limited risk stratification. Targeting the therapeutic approaches to patients at high risk of MACE who have imaging-identified vulnerable plaques (rather than simply hemodynamically significant CAD) might increase the absolute risk reduction achieved with these therapies and avoid unnecessary treatment of patients at lower risk. In addition, further research is necessary to provide better identification of which patients or coronary lesions can mostly benefit from invasive or noninvasive imaging evaluation for detection of vulnerable plaques, optimal risk stratification, and the application of preventive PCI. Furthermore, the regional difference of vulnerable plaques would be of interest for future research because of the generalizability of the data generated from Asia.

CONCLUSIONS

Over several decades, the optimal target of PCI has been ischemia-inducing, flow-limiting obstructive CAD. Nevertheless, several long-term follow-up studies have shown that adverse cardiovascular events can occur in nonflow-limiting lesions. Novel noninvasive and invasive imaging modalities have allowed early and improved identification of vulnerable plaques in patients with CCS and patients with ACS. In particular, multiple prospective studies with diverse intracoronary imaging modalities (conventional or radiofrequency IVUS, NIRS-IVUS, and OCT)

have showed that high-risk plaque with typical imaging characteristics at increased risk of causing adverse events during long-term follow-up can be identified. Guideline-directed OMT has been fundamental for the secondary prevention of unexpected adverse cardiovascular events because of vulnerable plaques and several pharmacologic therapies has demonstrated its efficacy on the regression of atherosclerotic plaques. Although OMTs are foundational therapies for the secondary prevention of cardiovascular disease in patients with established coronary atherosclerosis, the incidences of coronary death, MI, and ACS continue to be unacceptably high. Therefore, a knowledge gap still remains between what is known and how to treat the vulnerable plaque in patients with stable angina or ACS (**Central Illustration**). Resolving several unmet issues on diagnosis and management of vulnerable plaques may improve patients' prognosis, avoiding recurrent ACS or unexpected cardiac deaths. Finally, whether several approaches can improve clinical outcomes by guiding pharmacotherapy intensification or prophylactic revascularization, without increasing unnecessary risks, can be answered only by large-scale RCTs.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Khan MA, Hashim MJ, Mustafa H, et al. Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. *Cureus*. 2020;12(7):e9349.

2. Bueno H. Epidemiology of acute coronary syndromes. In: James S, Camm AJ, Lüscher TF, Maurer G, Serruys PW, eds. *The ESC Textbook of Cardiovascular Medicine*. Oxford University Press; 2018.

3. Alderman EL, Corley SD, Fisher LD, et al. CASS Participating Investigators and Staff. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). *J Am Coll Cardiol*. 1993;22(4):1141–1154.

4. Lee JM, Choi KH, Koo B-K, et al. Prognostic implications of plaque characteristics and stenosis severity in patients with coronary artery disease. *J Am Coll Cardiol*. 2019;73(19):2413–2424.

5. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364(3):226–235.

6. Erlinge D, Maehara A, Ben-Yehuda O, et al. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet*. 2021;397(10278):985–995.

7. Cho YK, Hwang J, Lee CH, et al. Influence of anatomical and clinical characteristics on long-term prognosis of FFR-guided deferred coronary lesions. *J Am Coll Cardiol Intv*. 2020;13(16):1907–1916.

8. Kedhi E, Berta B, Roleder T, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J*. 2021;42(45):4671–4679.

9. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation*. 1989;79(4):733–743.

10. Tomaniak M, Katagiri Y, Modolo R, et al. Vulnerable plaques and patients: state-of-the-art. *Eur Heart J*. 2020;41(31):2997–3004.

11. Stone GW, Maehara A, Mintz GS. The reality of vulnerable plaque detection. *J Am Coll Cardiol Img*. 2011;4(8):902–904.

12. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. *J Am Coll Cardiol Img*. 2011;4(8):894–901.

13. Cheng JM, Garcia-Garcia HM, de Boer SP, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. *Eur Heart J*. 2014;35(10):639–647.

14. Xing L, Higuma T, Wang Z, et al. Clinical significance of lipid-rich plaque detected by optical coherence tomography: a 4-year follow-up study. *J Am Coll Cardiol*. 2017;69(20):2502–2513.

15. Waksman R, Di Mario C, Torguson R, et al. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. *Lancet*. 2019;394(10209):1629–1637.

16. Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J*. 2020;41(3):383–391.

17. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407–477.

18. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289–1367.

19. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21–e129.

20. Rodés-Cabau J, Bertrand OF, Larose E, et al. Comparison of plaque sealing with paclitaxel-eluting stents versus medical therapy for the treatment of moderate nonsignificant saphenous vein graft lesions: the moderate vein graft lesion stenting with the taxus stent and intravascular ultrasound (VELETI) pilot trial. *Circulation*. 2009;120(20):1978–1986.

21. Wykrzykowska JJ, Diletti R, Gutierrez-Chico JL, et al. Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT). *EuroIntervention*. 2012;8(8):945–954.

22. Mol JQ, Bom MJ, Damman P, Knaapen P, van Royen N. Pre-emptive OCT-guided angioplasty of vulnerable intermediate coronary lesions: results from the prematurely halted PECTUS-Trial. *J Interv Cardiol*. 2020;2020:8821525.

23. Stone GW, Maehara A, Ali ZA, et al. Percutaneous coronary intervention for vulnerable coronary atherosclerotic plaque. *J Am Coll Cardiol*. 2020;76(20):2289–2301.

24. Räber L, Mintz GS, Koskinas KC, et al. Clinical use of intracoronary imaging. Part 1: guidance and

optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. 2018;39(35):3281–3300.

25. Honda S, Kataoka Y, Kanaya T, Noguchi T, Ogawa H, Yasuda S. Characterization of coronary atherosclerosis by intravascular imaging modalities. *Cardiovasc Diagn Ther*. 2016;6(4):368–381.

26. Suh WM, Seto AH, Margey RJP, Cruz-Gonzalez I, Jang I-K. Intravascular detection of the vulnerable plaque. *Circ Cardiovasc Imaging*. 2011;4(2):169–178.

27. Dawson LP, Lum M, Nerleker N, Nicholls SJ, Layland J. Coronary atherosclerotic plaque regression. *J Am Coll Cardiol*. 2022;79(1):66–82.

28. Prati F, Regar E, Mintz GS, et al. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J*. 2009;31(4):401–415.

29. Sandfort V, Lima JAC, Bluemke DA. Noninvasive imaging of atherosclerotic plaque progression. *Circ Cardiovasc Imaging*. 2015;8(7):e003316.

30. Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J*. 2019;41(3):383–391.

31. Kubo T, Ino Y, Mintz GS, et al. Optical coherence tomography detection of vulnerable plaques at high risk of developing acute coronary syndrome. *Eur Heart J Cardiovasc Imaging*. 2021;22(12):1376–1384.

32. Jiang S, Fang C, Xu X, et al. Identification of high-risk coronary lesions by 3-vessel optical coherence tomography. *J Am Coll Cardiol*. 2023;81(13):1217–1230.

33. Mol JQ, Volleberg R, Belkacemi A, et al. Fractional flow reserve-negative high-risk plaques and clinical outcomes after myocardial infarction. *JAMA Cardiol*. 2023;8(11):1013–1021.

34. Gardner CM, Tan H, Hull EL, et al. Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. *J Am Coll Cardiol Img*. 2008;1(5):638–648.

35. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*. 2007;50(4):319–326.

36. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary ct angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II Trial. *J Am Coll Cardiol*. 2014;64(7):684–692.

37. Williams MC, Kwiecinski J, Doris M, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction. *Circulation*. 2020;141(18):1452–1462.

38. Otsuka K, Fukuda S, Tanaka A, et al. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *J Am Coll Cardiol Img*. 2013;6(4):448–457.

39. Kröner ESJ, van Velzen JE, Boogers MJ, et al. Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. *Am J Cardiol*. 2011;107(12):1725–1729.

40. Gaba P, Gersh BJ, Muller J, Narula J, Stone GW. Evolving concepts of the vulnerable atherosclerotic plaque and the vulnerable patient: implications for patient care and future research. *Nat Rev Cardiol*. 2023;20(3):181–196.

41. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111–188.

42. Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome. *Circulation*. 2004;110(9):1061–1068.

43. Räber L, Taniwaki M, Zaugg S, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. *Eur Heart J*. 2014;36(8):490–500.

44. Hiro T, Kimura T, Morimoto T, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome. *J Am Coll Cardiol*. 2009;54(4):293–302.

45. Park S-J, Kang S-J, Ahn J-M, et al. Effect of statin treatment on modifying plaque composition. *J Am Coll Cardiol*. 2016;67(15):1772–1783.

46. Komukai K, Kubo T, Kitabata H, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: the EASY-FIT study. *J Am Coll Cardiol*. 2014;64(21):2207–2217.

47. Nishiguchi T, Kubo T, Tanimoto T, et al. Effect of early pitavastatin therapy on coronary fibrous-cap thickness assessed by optical coherence tomography in patients with acute coronary syndrome. *J Am Coll Cardiol Img*. 2018;11(6):829–838.

48. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295(13):1556–1565.

49. Takayama T, Hiro T, Yamagishi M, et al. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese Subjects (COSMOS). *Circ J*. 2009;73(11):2110–2117.

50. Kini AS, Baber U, Kovacic JC, et al. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy). *J Am Coll Cardiol*. 2013;62(1):21–29.

51. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291(9):1071–1080.

52. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med*. 2011;365(22):2078–2087.

53. Tsujita K, Sugiyama S, Sumida H, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention. *J Am Coll Cardiol*. 2015;66(5):495–507.

54. Nakajima N, Miyauchi K, Yokoyama T, et al. Effect of combination of ezetimibe and a statin on coronary plaque regression in patients with acute coronary syndrome: ZEUS trial (eZEtimibe Ultrasound Study). *IJC Metabolic and Endocrine*. 2014;3:8–13.

55. Hougaard M, Hansen HS, Thayssen P, et al. Influence of ezetimibe in addition to high-dose atorvastatin therapy on plaque composition in patients with ST-segment elevation myocardial infarction assessed by serial: intravascular ultrasound with iMap: the OCTIVUS trial. *Cardiovascular Revascularization Medicine*. 2017;18(2):110–117.

56. Hibi K, Sonoda S, Kawasaki M, et al. Effects of ezetimibe-statin combination therapy on coronary atherosclerosis in acute coronary syndrome. *Circ J*. 2018;82(3):757–766.

57. Masuda J, Tanigawa T, Yamada T, et al. Effect of combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease. *Int Heart J*. 2015;56(3):278–285.

58. Kovarnik T, Mintz GS, Skalicka H, et al. Virtual histology evaluation of atherosclerosis regression during atorvastatin and ezetimibe administration: HEAVEN Study. *Circ J*. 2012;76(1):176–183.

59. Ueda Y, Hiro T, Hirayama A, et al. Effect of ezetimibe on stabilization and regression of intracoronary plaque—the ZIPANGU study. *Circ J*. 2017;81(11):1611–1619.

60. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489–1499.

61. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713–1722.

62. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379(22):2097–2107.

63. Ako J, Hibi K, Tsujita K, et al. Effect of alirocumab on coronary atheroma volume in Japanese patients with acute coronary syndrome—The ODYSSEY J-IVUS Trial. *Circ J*. 2019;83(10):2025–2033.

64. Nicholls SJ, Kataoka Y, Nissen SE, et al. Effect of evolocumab on coronary plaque phenotype and

burden in statin-treated patients following myocardial infarction. *J Am Coll Cardiol Img*. 2022;15(7):1308–1321.

65. Räber L, Ueki Y, Otsuka T, et al. Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI Randomized Clinical Trial. *JAMA*. 2022;327(18):1771–1781.

66. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA*. 2016;316(22):2373–2384.

67. Hirai K, Imamura S, Hirai A, Ookawara S, Morishita Y. Effect of evolocumab on vulnerable coronary plaques: a serial coronary computed tomography angiography study. *J Clin Med*. 2020;9(10):3338.

68. Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J Am Coll Cardiol*. 2009;54(7):585–594.

69. Mozaffarian D, Wu JHY. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;58(20):2047–2067.

70. Watanabe T, Ando K, Daidoji H, et al. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. *J Cardiol*. 2017;70(6):537–544.

71. Alfaddagh A, Elajami TK, Ashfaque H, Saleh M, Bistrian BR, Welty FK. Effect of eicosapentaenoic and docosahexaenoic acids added to statin therapy on coronary artery plaque in patients with coronary artery disease: a randomized clinical trial. *J Am Heart Assoc*. 2017;6(12):e006981.

72. Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;41(40):3925–3932.

73. Motoyama S, Nagahara Y, Sarai M, et al. Effect of omega-3 fatty acids on coronary plaque morphology - a serial computed tomography angiography study. *Circ J*. 2022;86(5):831–842.

74. Nishio R, Shinke T, Otake H, et al. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. *Atherosclerosis*. 2014;234(1):114–119.

75. Kita Y, Watanabe M, Kamon D, et al. Effects of fatty acid therapy in addition to strong statin on coronary plaques in acute coronary syndrome: an optical coherence tomography study. *J Am Heart Assoc*. 2020;9(16):e015593.

76. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340(2):115–126.

77. Imazio M, Nidorf M. Colchicine and the heart. *Eur Heart J*. 2021;42(28):2745–2760.

78. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol*. 2013;61(4):404–410.

79. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020;383(19):1838–1847.

80. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Revista Española de Cardiología (English Edition)*. 2022;75(5):429.

81. Vaidya K, Arnott C, Martínez GJ, et al. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome. *J Am Coll Cardiol Img*. 2018;11(2_Part_2):305–316.

82. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382(15):1395–1407.

83. Chacko L, Howard JP, Rajkumar C, et al. Effects of percutaneous coronary intervention on death and myocardial infarction stratified by stable and unstable coronary artery disease. *Circ Cardiovasc Qual Outcomes*. 2020;13(2):e006363.

84. Navarese EP, Lansky AJ, Kereiakes DJ, et al. Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis. *Eur Heart J*. 2021;42(45):4638–4651.

85. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. *N Engl J Med*. 2004;350(15):1495–1504.

86. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the Vulnerable Plaque. *J Am Coll Cardiol*. 2006;47(Suppl 8):C13–C18.

87. Pinilla-Echeverri N, Mehta SR, Wang J, et al. Nonculprit lesion plaque morphology in patients with ST-segment–elevation myocardial infarction. *Circ Cardiovasc Interv*. 2020;13(7):e008768.

88. Brugaletta S, Radu MD, Garcia-Garcia HM, et al. Circumferential evaluation of the neointima by optical coherence tomography after ABSORB bioresorbable vascular scaffold implantation: can the scaffold cap the plaque? *Atherosclerosis*. 2012;221(1):106–112.

89. Bourantas CV, Papafaklis MI, Kotsia A, et al. Effect of the endothelial shear stress patterns on neointimal proliferation following drug-eluting bioresorbable vascular scaffold implantation: an optical coherence tomography study. *J Am Coll Cardiol Intv*. 2014;7(3):315–324.

90. Ahn JM, Kang DY, Lee PH, et al. Preventive PCI or medical therapy alone for vulnerable atherosclerotic coronary plaque: rationale and design of the randomized, controlled PREVENT trial. *Am Heart J*. 2023;264:83–96.

91. van Veelen A, Küçük IT, Fuentes FH, et al. First-in-human drug-eluting balloon treatment of vulnerable lipid-rich plaques: rationale and design of the DEBuT-LRP Study. *J Clin Med*. 2023;12(18):5807.

92. Verheye S, Roth L, De Meyer I, et al. Cryotherapy increases features of plaque stability in atherosclerotic rabbits. *EuroIntervention*. 2016;12(6):748–756.

93. Jain M, Zellweger M, Wagnières G, van den Bergh H, Cook S, Giraud MN. Photodynamic therapy for the treatment of atherosclerotic plaque: lost in translation? *Cardiovasc Ther*. 2017;35(2).

94. Stone GW, Maehara A, Muller JE, et al. Plaque characterization to inform the prediction and prevention of periprocedural myocardial infarction during percutaneous coronary intervention: the CANARY Trial (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow). *J Am Coll Cardiol Intv*. 2015;8(7):927–936.

95. Williams MC, Moss AJ, Dweck M, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART Study. *J Am Coll Cardiol*. 2019;73(3):291–301.

96. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. *JAMA Cardiol*. 2018;3(2):144–152.

97. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2018;40(2):87–165.

98. Kuramitsu S, Matsuo H, Shinozaki T, et al. Two-year outcomes after deferral of revascularization based on fractional flow reserve: the J-CONFIRM Registry. *Circ Cardiovasc Interv*. 2020;13(1):e008355.

KEY WORDS intravascular imaging, percutaneous coronary intervention, pharmacology, vulnerable plaque