Journal of
Clinical Medicine

MDPI

Review

Prognostic Role and Therapeutic Implications of Intravascular Optical Coherence Tomography Detected Coronary Plaque Microstructures in Patients with Coronary Artery Disease

Michele Russo [1,*], Elena Bacigalupi [1], Francesco Radico [1], Luca Scorpiglione [1], Filippo Luca Gurgoglione [2], Alessandro Russo [3], Carlo Vigna [3], Mattia Galli [4,5], Stefano Benenati [6], Rocco Vergallo [7,8], Rocco Antonio Montone [9,10], Umberto Benedetto [11], Giampaolo Niccoli [2], Francesco Prati [12,13] and Marco Zimarino [1,14]

1 Department of Cardiology, SS. Annunziata Hospital, ASL2 Abruzzo, Via dei Vestini, 66100 Chieti, Italy; elenabaci96@gmail.com (E.B.); francescoradico@hotmail.it (F.R.); lscorpi94@gmail.com (L.S.); m.zimarino@unich.it (M.Z.)
2 Department of Medicine, University of Parma, 43125 Parma, Italy; filippolucagurgoglione@gmail.com (F.L.G.); gniccoli73@hotmail.it (G.N.)
3 Cardiology Unit, Fondazione IRCCS Casa Sollievo della Sofferenza, 71013 San Giovanni Rotondo, Italy; alessandrorusso17@hotmail.it (A.R.); cvigna57@gmail.com (C.V.)
4 Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, 04100 Latina, Italy; dottormattiagalli@gmail.com
5 Maria Cecilia Hospital, GVM Care & Research, 48033 Cotignola, Italy
6 Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, IRCCS Italian Cardiology Network, 16132 Genova, Italy; stefanobenenatimd@gmail.com
7 Interventional Cardiology Unit, Cardiothoracic and Vascular Department (DICATOV), IRCCS Ospedale Policlinico San Martino, 16132 Genova, Italy; roccovergallo@gmail.com
8 Department of Internal Medicine and Medical Specialties (DIMI), Università di Genova, 16132 Genova, Italy
9 Department of Cardiovascular and Pulmonary Sciences, Catholic University of the Sacred Heart, 00168 Rome, Italy; rocco.montone@gmail.com
10 Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Rome, Italy
11 Department of Cardiac Surgery, University "G. d'Annunzio", 66100 Chieti, Italy; umberto.benedetto@asl2abruzzo.it
12 Department of Cardiovascular Sciences, San Giovanni Addolorata Hospital, 00184 Rome, Italy; fprati61@gmail.com
13 Centro per la Lotta Contro L'Infarto—CLI Foundation, 00182 Rome, Italy
14 Department of Neuroscience, Imaging and Clinical Sciences, "Gabriele d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy
* Correspondence: michelerusso0509@gmail.com; Tel.: +39-0871-358240; Fax: +39-0871-358487

check for updates

Academic Editor: Anna Kabłak-Ziembicka

Received: 15 October 2025
Revised: 11 November 2025
Accepted: 15 November 2025
Published: 17 November 2025

Citation: Russo, M.; Bacigalupi, E.; Radico, F.; Scorpiglione, L.; Gurgoglione, F.L.; Russo, A.; Vigna, C.; Galli, M.; Benenati, S.; Vergallo, R.; et al. Prognostic Role and Therapeutic Implications of Intravascular Optical Coherence Tomography Detected Coronary Plaque Microstructures in Patients with Coronary Artery Disease. *J. Clin. Med.* **2025**, *14*, 8132. https://doi.org/10.3390/jcm14228132

Abstract

Intracoronary optical coherence tomography (OCT) is a highly accurate and sensitive imaging tool capable of providing high resolution visualization of atherosclerotic coronary plaque morphology and microstructures in vivo. OCT has proven to be useful in clinical practice, particularly in percutaneous coronary intervention (PCI) guidance, assessment of stent-related complications, and elucidation of the pathobiological cause of acute coronary syndrome. Notably, OCT allows for the detection of specific plaque features (i.e., thin cap fibroatheroma, lipid-rich plaque, macrophage infiltration, healed plaques, microvessels, etc.) that are known to carry prognostic significance in the context of coronary artery disease (CAD). These insights may offer valuable information about the patient's overall atherosclerotic background, potentially supporting more personalized secondary prevention strategies, including lifestyle modification and targeted pharmacologic therapies. Recently, the role of preventive PCI in plaques with high-risk features has also been investigated with promising—though still preliminary—results. In this narrative review, we primarily aim to discuss studies evaluating the prognostic value of OCT-identified

coronary plaque microstructures. We also assessed potential therapeutic implications in the management of patients with CAD.

Keywords: plaque microstructures; atherosclerosis; coronary artery disease; vulnerable plaque; prognosis; optical coherence tomography

1. Introduction

Ischemic heart disease (IHD) is the leading cause of admission to intensive cardiac care units and death worldwide, and its absolute prevalence is expected to increase in the future, mainly because of population aging. In particular, it has been forecasted that IHD will cause 186.5 million of all-age disability-adjusted life-years (DALYs) and about 10.6 million of all-age deaths in 2050 [1,2]. Coronary atherosclerosis is the main cause of coronary artery disease (CAD) and IHD, and the study of CAD pathophysiology and consequent therapeutic implications represents the main topic of current research on IHD.

Intracoronary optical coherence tomography (OCT) is a highly sensitive and accurate diagnostic tool performed during coronary angiography that is able to study coronary plaque walls and microstructures in vivo [3]. OCT uses near-infrared light (wavelength of about 1.3 μm) to produce high resolution images (axial resolution is between 10 and 15 μm) generated by assessing the time delay of the light reflected or backscattered from the tissues (the vessel wall in the case of intravascular OCT) and from a predefined distance as a reference with a technique known as interferometry. The different properties of attenuation of the light by the tissues (i.e., lipid, calcium) are responsible for their diverse appearance in OCT images and define OCT penetration depth at these sites [3].

OCT, owing to its superior spatial resolution, has shown reliable diagnostic performance in elucidating the underlying pathobiological mechanisms of acute coronary syndrome (ACS), in assessing the causes of stent-related complications, and in guiding percutaneous coronary intervention (PCI) [4–7]. Notably, plaque microstructures imaged during OCT runs (i.e., thin-cap fibroatheroma—TCFA, lipid-rich plaques, healed plaques, microchannels, macrophage infiltration, etc.) have a documented prognostic relevance and are specific targets of preventive measures [8]. The beneficial role of preventive PCI has also shown promising results in the pioneering PREVENT study [9].

In recent years, numerous studies have investigated the prognostic impact of OCT-detected plaque features. Nevertheless, despite several reviews addressing the vulnerability characteristics of coronary plaque microstructures, to date no comprehensive review has summarized the existing evidence on their prognostic significance. Hereby, in this narrative review, we discuss the available data relative to the clinical significance of OCT-detected plaque microstructures in native coronary arteries. We also discuss possible therapeutic strategies for plaque stabilization and reduction of plaque-related future cardiovascular (CV) events.

2. Prognostic Significance of Plaque Microstructures Identified by OCT Imaging

An inclusive search of electronic databases, including PubMed, EMBASE, Web of Science, and Google Scholar, was performed to identify studies published from January 2010 to September 2025 assessing the relationship between OCT-detected plaque microstructures and clinical events at follow-up. References listed in the selected articles were also investigated. The following searched terms or phrases were used: “thin cap fibroatheroma and optical coherence tomography and events”, “thin cap fibroatheroma and optical coher-

ence tomography and prognosis"; "lipid and optical coherence tomography and events", "lipid and optical coherence tomography and prognosis"; "healed coronary plaque or layered coronary plaque and optical coherence tomography and events", "healed coronary plaque or layered coronary plaque and optical coherence tomography and prognosis"; "macrophage and optical coherence tomography and events", "macrophage and optical coherence tomography and prognosis"; "cholesterol crystal and optical coherence tomography and events", "cholesterol crystal and optical coherence tomography and prognosis"; "microvessel or microchannel or intimal vasculature and optical coherence tomography and events", "microvessel or microchannel or intimal vasculature and optical coherence tomography and prognosis"; "calcification or calcium or calcified nodule and optical coherence tomography and events", "calcification or calcium or calcified nodule and optical coherence tomography and prognosis"; "plaque rupture and optical coherence tomography and events", "plaque rupture and optical coherence tomography and prognosis". Studies were considered eligible if (1) they included patients undergoing coronary angiography and concomitant intracoronary OCT imaging; (2) reported CV events at clinical follow-up; and (3) described an association between at least one coronary plaque microstructure as assessed by OCT and future CV events.

Figures 1–3 show the OCT appearance of different examined plaque microstructures. Table S1 summarizes the studies assessing the prognostic impact of coronary plaque features evaluated by intracoronary OCT imaging.

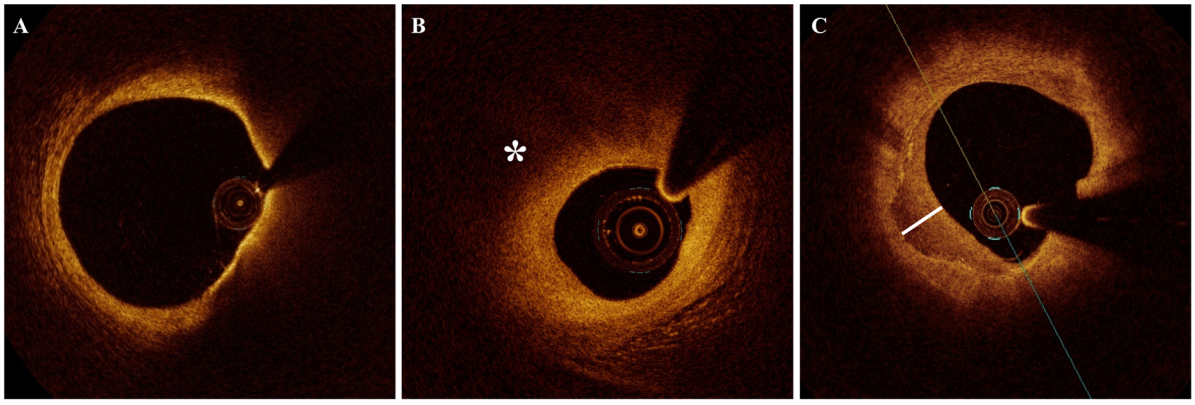

Figure 1. OCT imaging of TCFA, lipid-rich plaque, and healed plaque. (**A**) TCFA; (**B**) lipid-rich plaque (asterisk indicates lipid pool); (**C**) healed plaque (line indicates the layer of tissue). OCT = optical coherence tomography; TCFA = thin cap fibroatheroma.

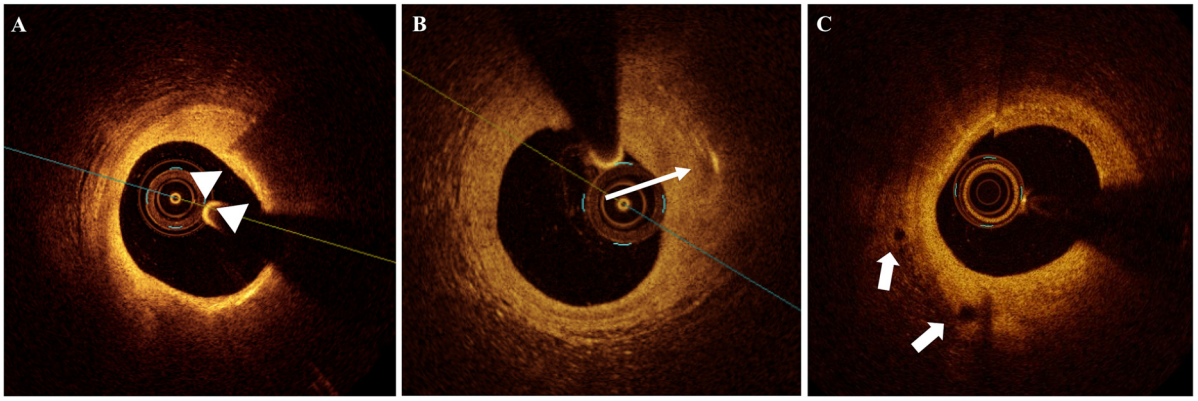

Figure 2. OCT imaging of MØI, CCs, and microvessels. (**A**) MØI (indicated by arrowheads); (**B**) presence of CCs (indicated by arrow); (**C**) microvessels (indicated by arrows). CCs = cholesterol crystals; MØI = macrophage infiltration; OCT = optical coherence tomography.

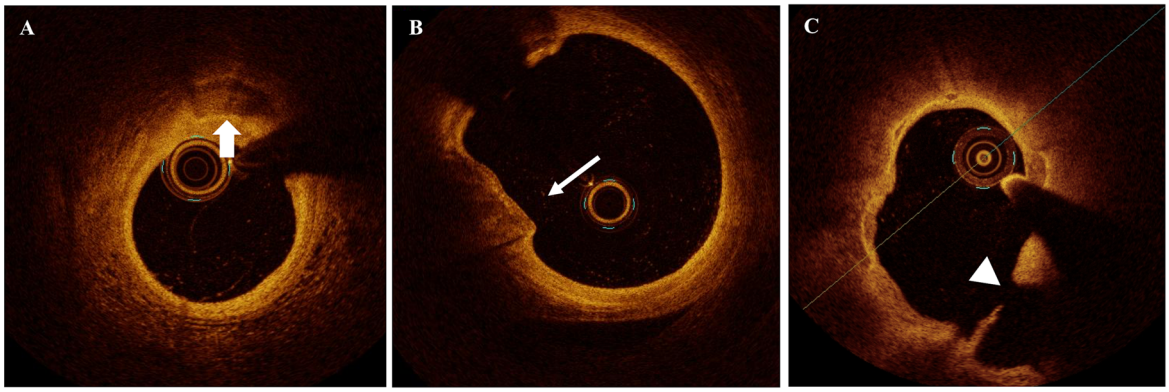

Figure 3. OCT imaging of spotty calcification, calcified nodule, and previous rupture. (**A**) spotty calcification (indicated by arrow); (**B**) CN (indicated by arrow); (**C**) previous plaque rupture (cavity is indicated by arrowheads). CN = calcified nodules; OCT = optical coherence tomography.

2.1. TCFA

According to histological studies, TCFA is considered the prototype of vulnerable plaques and the precursor of plaque rupture [10]. In histology samples, it is usually characterized by large necrotic cores covered by a thin layer of fibrous tissue (representing the fibrous cap), high macrophage and lymphocyte intimal infiltration, and deficient smooth muscle cells (SMCs) [11,12]. In a post-mortem study, Burke et al. [13] found that 95% of patients who died suddenly from coronary thrombosis due to plaque rupture had a fibrous cap < 65 μm. The proximal sites of major epicardial arteries, in particular the left descending artery (LAD), are the most frequent sites of TCFA localization in pathology and intravascular imaging studies [10,14]. OCT imaging showed a high ability to identify TCFA, defined as a lipid plaque having a lipid arc in circumference >90° enclosed by a fibrous cap under a definite threshold (Figure 1A). A minimal cut-off of 65 μm is usually adopted to define a fibrous cap as thin at OCT imaging, although different values have been used by other studies [3]. OCT studies reported that TCFAs have been related to plaque rupture and have been associated with other "vulnerable" plaque features such as macrophage infiltration (MØI), microvessels, and cholesterol crystals [15–18]. TCFA has also been associated with higher pericoronary adipose tissue attenuation (PCAT) [19] and higher levels of blood markers of systemic inflammation [20], thus suggesting a relationship between TCFA and inflammation.

TCFA as assessed by OCT imaging has been strongly associated with future CV events [8,21–28]. In a recent OCT-imaged three-epicardial coronary vessel study including 1312 ACS patients with five-year follow-up, Dai et al. [21] reported that TCFA (defined as lipid plaque with maximum lipid arc > 180° and thinnest fibrous cap thickness (FCT) < 65 μm) in non-culprit lesions (NCL) was associated with increased risk of patient-level NCL-related major adverse CV events (MACEs) (hazard ratio [HR] 2.50 [95% CI: 1.48–4.20]), enclosing a composite of cardiac death, non-fatal myocardial infarction (MI), and unplanned coronary revascularization. Biccirè et al. [22], in the long term follow-up of the Relationship Between OCT Coronary Plaque Morphology and Clinical Outcome (CLIMA) [8] study, including 1003 patients and evaluating the prognostic significance of OCT plaque features in untreated proximal LAD, reported that TCFA with FCT < 75 μm was strongly associated with the composite hard endpoint of cardiac death and target-segment MI (HR 3.46 [95% CI: 2.17–5.53]). Interestingly, in the COMBINE OCT-FFR, merging both hemodynamic interrogation by fractional flow reserve (FFR) and imaging assessment by OCT of coronary plaques in patients with diabetes mellitus, the presence of TCFA (defined as lipid-rich plaque with lipid arc > 90° and FCT ≤ 65 μm) in FFR-negative lesions was an independent predictor of future events (HR 2.89 [95% CI: 1.61–5.20]) in a follow-up time up

to 5 years [23]. Notably, a meta-analysis by Gallone et al. [24] confirmed these observations, showing that TCFA was associated with MACEs both at the patient-level and lesion-level. Finally, Yamaji et al. [27] reported that TCFA (defined as lipid plaque with minimum FCT $\leq$ 65 μm) was significantly associated with a more than 2-fold higher three-year risk of ischemia-driven non-target vessel revascularization, primarily related to revascularization in the imaged region. Accordingly, it is important to emphasize that not all TCFAs that have undergone destabilization cause ACS. Plaque healing may occur, and the generation of a new layer of tissue may favor plaque growth and negative vessel remodeling [29,30]. In this regard, serial OCT studies reported that TCFA was a strong predictor of plaque progression [31,32], and was associated with the presence of healed plaques [33].

2.2. Lipid-Rich Plaque and Lipid Burden

Lipids are identified by OCT imaging as signal-poor regions with diffuse borders and high attenuation properties with an overlying signal-rich band with discrete margins representing the fibrous cap [3] (Figure 1B). Considering the high attenuation features, penetration depth at lipid sites is markedly reduced, impairing the ability of OCT to assess structures behind lipid pools.

Previous histopathological validation studies reported high agreement of lipid assessment between OCT and pathology specimens [34].

Lipid-rich plaques (LRP) in OCT imaging are usually defined as plaques with a circumferential lipid arc > 90°. Semiquantitative measures such as lipid arc, lipid length, and lipid index (mean lipid arc x lipid length) are usually used to calculate OCT-imaged lipid burden [3]. In a previous three-vessel OCT study in patients with CAD, a prevalence of 1.3 LRP per patient was reported, and patients with ACS showed higher lipid burden than those with stable angina [35]. LRP has been associated with plaque features such as MØI, microvessels, and healed plaques [17,33,36]. Moreover, LRP was found to be an independent predictor of rapid plaque and calcification progression [31,37].

Many OCT investigations assessed the prognostic impact of LRP and lipid burden, mainly showing a relationship between these features and future CV events [8,22,26,38–40]. Xing et al. [38], in a four-year follow-up study of patients undergoing PCI, reported that LRP in NCL of the target vessel was associated with increased non-culprit lesion MACE (HR 2.06 [95% CI: 1.05–4.04]), defined as a composite of cardiac death, acute MI, and ischemia-driven revascularization. In the study, a larger lipid burden in LRP was found in patients with non-culprit MACE. Kubo et al. [26], in a study including 1378 patients with a median follow-up period of 6 years, similarly reported that LRP at a non-culprit lesion was strongly significantly associated with future ACS (HR 12.67 [95% CI: 6.82–23.57]) attributed to a non-culprit plaque imaged by OCT at baseline. Importantly, in the previously cited CLIMA study and its five-year follow-up report, lipid plaques in the proximal LAD with lipid arc circumferential extension >180° had increased risk of future events (HR 2.4 [95% CI: 1.2–4.8]; HR 2.2 [95% CI: 1.4–3.5], respectively) [8,22]. Another study derived from the CLIMA assessing the use of automated software to calculate lipid burden reported that the automated maximum OCT-derived lipid core burden index (LCBI) in 4 mm predicted CV events and was associated with vulnerable plaque features [39]. Interestingly, in a report from the COMBINE OCT-FFR trial, Fabris et al. [40] suggested that, in 390 diabetic patients undergoing OCT of non-ischemic lesions, TCFA had a stronger association with CV events than overall LRP, showing that thick-cap fibroatheroma LRP had a similar risk of future events to non-LRP. Finally, many studies described the relationship between lipid plaque burden and worse PCI outcomes (mainly related to stent edge dissection, tissue protrusion, and incomplete apposition), reduced Thrombolysis in Myocardial Infarction (TIMI) flow

post-PCI, and periprocedural biomarker elevation, the latter probably due to lipid debris distal embolization [34].

2.3. Healed Plaques

Healed coronary plaques are lesions presenting signs of previous plaque destabilization undergoing a healing process. Also called "layered plaques" for their appearance, they are defined at OCT imaging as plaques presenting one or more layers with different optical densities and a clear demarcation from underlying components [33] (Figure 1C). A recent pathology-OCT validation study reported high agreement between OCT imaging and histology in healed plaque identification, paving the way to the study of this plaque phenotype in vivo [41,42]. In histology studies, healed lesions have been found in the coronary arteries of >50% of patients dying suddenly from coronary death who had no evidence of previous MI and have been described at sites with greater luminal stenosis, suggesting their role in plaque growth and vessel luminal narrowing [43,44]. Accordingly, OCT studies reported that healed plaques were associated with higher stenosis severity and plaque vulnerability (more TCFA, lipid plaques, and macrophages) and were found to independently predict rapid plaque progression [29,31,33,45]. Stable angina pectoris (SAP), multivessel disease, complex lesion, and diameter stenosis >70% were found to be independent predictors of healed plaque at the culprit lesion in a previous study [46].

Several recent OCT studies have evaluated the clinical significance of healed plaques in the coronary arteries, demonstrating a strong association between healed lesions and the need for future PCI [8,47–57]. In the study by Kurihara et al. [47] including 265 patients with either ACS or SAP, those with healed coronary plaques had a higher future revascularization rate at two-year follow-up (odds ratio [OR] 3.096 [95% CI 1.148–8.356]) but similar "hard outcomes" of cardiac death and ACS than those without healed lesions. In another recent report by Yi et al. [48] studying 553 NCL in ACS patients followed up for 6 years, the authors found similar results, showing that patients with new layered lesions at follow-up had a higher risk of NCL-MACEs (HR 2.52 [95% CI 1.20–5.33]), mainly determined by non-culprit-plaque-related coronary revascularization. Other studies confirmed the association between healed plaques and increased risk of revascularization, showing similar outcomes about future ACS, cardiac death, or death from any cause [49–51]. Fracassi et al. reported increased prevalence of all-cause rehospitalization in patients with ACS with culprit healed lesions, while no differences in the rate of future death, ACS, or revascularization were found between the groups [52]. On the other hand, other reports with shorter follow-up found no differences in clinical outcomes between patients with and without healed plaques [53–55]. In the CLIMA study, having as a primary endpoint a composite of cardiac death and target segment MI, healed plaques were not associated with the main outcome [8]. Interestingly, in a prospective clinical follow-up study, patients with recurrent ACS had the lowest prevalence of healed lesions as opposed to those with single acute MI and those with long-standing SAP [56]. Accordingly, a dual significance of healed plaques in the coronary arteries has been suggested: although healed plaques are signs of plaques undergoing previous destabilization, patients with these features may have a more effective plaque healing process with greater protection against occlusive thrombosis and recurrent ACS. On the other hand, plaque healing, through thrombus organization and deposition of new layer of fibrous tissue, may contribute to plaque progression, negative vessel remodeling and ischemia, potentially requiring future revascularization [30,31,42]. Finally, regarding post-PCI outcomes, healed plaques have been associated with reduced stent expansion ratio and mean stent eccentricity index, potentially requiring more aggressive balloon dilatation to obtain optimal stent results [57].

2.4. Macrophage Infiltration (MØI)

Coronary plaque inflammation is thought to play a key role in the mechanisms of plaque growth and plaque rupture, with macrophages representing the major inflammatory cells involved in the process. In histology studies including patients who died from sudden coronary death, macrophages have been colocalized with ruptured plaques and with occlusive thrombi [10]. A previous study comparing OCT and pathology reported that OCT can identify sites of the fibrous cap with high macrophage density, appearing as punctate sites with high reflecting properties [58]. The use of normalized standard deviation (NSD) for quantifying MØI has been proposed, as it shows an excellent correlation with the percentage of CD68 staining in fibroatheroma; however, alternative approaches have also been described [58–62]. MØI are conventionally defined in OCT imaging as signal-rich, distinct, or confluent punctate regions that exceed the intensity of background speckle noise with a dark shadow behind aggregates [3] (Figure 2A). According to the validation study valuing macrophage density into the fibrous cap, MØI should be assessed only in fibroatheromas [3,58]. Macrophage density measured by OCT was found to be higher in unstable patients, and surface MØI was related to unstable clinical presentations [63]. In addition, macrophage density was higher in TCFA and was found to positively correlate with baseline white blood cell count and LRP and inversely relate to fibrous cap thickness [16]. High C-reactive protein was also independently associated with MØI within the culprit plaques in ACS patients in another study [64], and PCAT was found to be higher in patients with culprit plaque MØI [65].

Clinical studies have confirmed the relationship between MØI and adverse CV outcomes [8,22,66–70]. The previously referenced CLIMA study reported that at both one-year and five-year follow-up, OCT-identified MØI in the untreated proximal LAD was associated with increased risk of hard events (HR 2.7 [95% CI: 1.2–6.1]; HR: 1.81 [95% CI: 1.09–3.01], respectively) [8,22]. In a sub-study of the CLIMA, the prognostic role of macrophage burden was also assessed, and large macrophage arcs (>67°) and superficial macrophages (defined as a distance from intima-lumen contour to macrophage string < 0.12 mm) were found to be independent predictors of the main outcome [66]. In the OCT-FORMIDABLE study examining 209 patients with ACS undergoing OCT imaging, necrotic core with MØI in the culprit lesion was an independent predictor of the composite endpoint of death from cardiac causes, non-fatal MI, and clinically driven target vessel revascularization at a median follow-up of 12.6 months (HR 3.3 [95% CI: 1.6–6.6]) [67]. Colocalization of MØI and calcifications has also been related to future events [68]. In a prospective study, Fracassi et al. found that, among 156 ACS patients, MØI in the culprit plaque was an independent predictor of recurrent ACS (OR 3.145 [95% CI: 1.458–9.587]) at three-year follow-up [69]. Conversely, in another study of patients with stable CAD undergoing OCT imaging of the culprit vessel, MØI were not associated with future adverse CV outcomes [20]. Finally, Montone et al. reported that, in ACS patients with plaque erosion as the pathobiological mechanism of ACS, those with MØI at the culprit site had worse outcomes than those without MØI (HR 2.95 [95% CI: 1.09–8.02]), mainly driven by cardiac death and future revascularization in the target vessel and in the non-target lesions (median follow-up of 2.5 years) [70].

2.5. Cholesterol Crystals (CCs)

Cholesterol crystals (CCs) are the product of free cholesterol crystallization both in foam cells and in the extracellular space of atherosclerotic plaque intima derived from an imbalance in cholesterol homeostasis [71]. It has been demonstrated that CCs may trigger local inflammation by induction of the complement cascade and activation of the pyrin domain–containing 3 (NLRP3) inflammasome. In addition, pathology studies visualized

sharp-tipped CCs perforating the fibrous cap and reported that CCs were associated with plaque disruption, plaque thrombosis, and plaque size, suggesting their potential role in plaque progression and destabilization [72,73].

OCT validation studies showed that the sensibility of OCT as compared to pathology to identify CCs was 26% and 68%, although its specificity was higher (100% and 92%, respectively) [74,75]. CCs are classically defined at OCT imaging as thin, linear regions of high intensity, usually in proximity to a lipid-rich plaque [3] (Figure 2B). The absence of back shadow behind the high-intensity regions helps to differentiate CCs from MØI. In OCT studies, CCs have been associated with coronary plaque rupture and other microstructures such as TCFA, MØI, microvessels, and calcifications [76–78].

The prognostic significance of CCs as assessed by OCT imaging in CAD patients has been reported by some studies, which showed heterogeneous results [8,22,79–81]. Fujiyoshi et al. [79] investigated the clinical impact of OCT-detected CCs at the culprit lesion in 340 CAD patients (both ACS and SAP) treated with PCI and followed up for 1 year. They found that the incidence of MACEs (defined as a composite of cardiac death, non-fatal MI, target and non-target vessel revascularization) was higher in patients with CCs at the culprit lesion (mainly driven by non-target vessel revascularization), although CCs did not independently predict MACEs when included in a model with other OCT features [79]. Similarly, in the CLIMA study, CCs were not associated with the composite outcome [8,22]. In a recent report from the OPTICO-ACS study program, Nelles et al. stated that among 346 ACS patients, those with CCs at the culprit lesion had an increased risk of MACE+ compared to those without CCs at two-year follow-up (HR 1.705 [95% CI: 1.025–2.838]) resulting mainly from higher rates of target vessel revascularization and higher rates of unstable or progressive angina [80]. Finally, Usui et al., studying 735 NCL in 566 patients with both ACS and SAP, found that patients with untreated NCL containing CCs and low-intensity areas without attenuation (hypothesized as representative of intraplaque hemorrhage) had an increased risk of NCL-MACEs (HR 3.09 [95% CI: 1.27–7.50], defined as a composite of cardiac death, MI, or ischemia-driven revascularization related to NCL, mainly caused by ischemia-driven revascularization at a mean follow-up of 2.5 years [81].

2.6. Microvessels

Plaque angiogenesis implies the formation of intimal neovessels, largely deriving from adventitial vasa vasorum, triggered by local plaque microenvironment. Newborn vessels contribute to "nourish" atherosclerotic lesions, favoring inflammatory cells, cytokines, and cholesterol entrance into the intima [82]. The rupture of the leaky walls of intimal microvessels may be responsible for intraplaque hemorrhage (IPH), causing abrupt plaque expansion, free cholesterol accumulation from erythrocyte membranes, increased oxidative stress, and local inflammation. Pathology studies reported that microvessel density was higher in ruptured plaques of human aorta, and it was increased in lesions with severe MØI, TCFAs, and at sites with IPH [83].

OCT imaging showed a discrete accuracy to identify microvessels (also defined as microchannels) as compared to pathology, described at OCT imaging as "signal-poor voids that are sharply delineated and can usually be followed in multiple contiguous frames" [3,84,85] (Figure 2C). An intravascular imaging study reported that microchannels were present in about 38% of lesions in CAD patients and were associated with intravascular ultrasound (IVUS)-assessed positive remodeling, OCT-detected TCFA, and elevated hs-CRP levels [86]. Microvessels were also associated with higher prevalence of intimal laceration, vulnerable plaque features, and increased risk of slow flow phenomenon after stent implantation [87]. In a study by Uemura et al., the presence of OCT-imaged microvessels at baseline in non-significant coronary plaques of 53 CAD patients predicted angiographic

plaque progression after seventh-month follow-up [88]. Similar findings about plaque progression were reported by other studies [32,89,90].

Some studies have investigated the relationship between plaque microvessels and future clinical outcomes with inconsistent results [8,21,22,26,51,56,91]. Xu et al. [91] investigated the clinical impact of microvessels assessed by using intracoronary OCT in 535 patients with CAD either undergoing or not undergoing PCI. They found that, among patients undergoing PCI with stent implantation (340 patients), those with intraplaque microvessels had higher prevalence of periprocedural MI (4.0% vs. 1.6%, $p < 0.005$) and intraprocedural no-reflow (24.0% vs. 1.6%, $p < 0.005$) than those without. Conversely, patients not undergoing PCI (195 patients) were followed up for a median of 3.2 years, and those with intraplaque microvessels showed higher prevalence of clinically driven target lesion revascularization (12.4% vs. 1.4%, $p < 0.001$) at follow-up [91]. Other studies did not find an association between OCT-assessed microvessels and "hard outcomes" such as future ACS, MI, recurrent ACS, and cardiac death [8,21,22,26,56]. Similarly, in a recent post-hoc analysis of the COMBINE OCT-FFR trial, microvessels were not associated with the primary composite outcome at five-year follow-up [51].

2.7. Calcifications

Calcification is a key feature of the atherosclerotic process and reflects different phases of plaque biology, contributing to atherosclerosis progression and plaque destabilization [92].

OCT imaging showed very high accuracy for the identification of intimal calcification, described as signal-poor regions with sharply delineated borders and limited shadowing [3,93] (Figure 3A). According to calcium arc and calcium length, different dimensional subtypes of calcium deposits (microcalcification, spotty calcification, and large calcifications) and quantification of calcium burden have been assessed by OCT imaging [94,95]. Intracoronary OCT can recognize calcified nodules (CN) (Figure 3B) and other calcified plaque subtypes reported as possible pathobiological mechanisms of ACS at the culprit lesions [96].

The role of calcification in clinical outcomes remains a matter of ongoing debate. Pathological data have shown that patients who died from myocardial infarction had more frequent calcifications compared with individuals without a history of CV disease who died from non-cardiac causes. However, calcification was not associated with plaque instability, and the overall calcium burden showed an inverse relationship with MØI [97]. In vivo studies (coronary computed tomography and intravascular imaging studies) confirmed these data, reporting higher prevalence of obstructive CAD in patients with elevated coronary artery calcium scores (CACs), but reduced grade of local inflammation and vulnerability in the case of extensive calcifications and high calcification burden [94,95,98]. About calcification subtypes, spotty calcifications have been more frequently found in ACS patients than SAP and have been related to high-risk plaque features and signs of vascular inflammation [99–101]. Modification of tensile stress of the vessel wall by small calcium gatherings has also been suggested as a possible factor favoring plaque disruption [102]. Calcium burden was also found to negatively correlate with positive remodeling [103], and calcifications were associated with plaque progression [104].

In agreement with this evidence, a dual clinical connotation of calcification in the coronary arteries has been hypothesized: small calcium burdens and deposits would reflect more biologically "active" plaques with a higher degree of local inflammation and increased risk of progression, while extensive and bulky calcifications would indicate more "stable" plaques in advanced stages of the atherosclerotic process, with lower inflammatory infiltrates and minor lipid burdens but more extended atherosclerotic disease [95,105].

Calcium nodules were reported in about 4.2% of coronary lesions (both in stable and ACS patients) and were more frequently found in the ostial or mid-right coronary artery in a previous study [106]. They were the cause of coronary thrombosis in 2–7% of patients with sudden death and were associated with age, hemodialysis, diabetes, and severe calcifications [10,106,107].

Many studies assessed the prognostic impact of calcifications on future MACEs [21,26,38,56,108–113]. In the previously cited large population study of Dai et al. with a median follow-up of 4.1 years, calcifications in untreated non-culprit coronary lesions were predictors of future events (HR 1.93 [95% CI: 1.10–3.37]) at the lesion-level, although no specific data about calcium burden and subtypes were stated in the study [21]. Conversely, no statistically significant differences in non-culprit plaque MACEs and ACS were described in non-culprit lesions with calcifications in other studies [26,38].

Among calcium subtypes, spotty calcifications have been associated with future events [108,109]. Nelles et al. [108] reported that among 155 ACS patients undergoing PCI, those with spotty calcifications at the culprit lesion had worse outcomes (HR 3.29 [95% CI: 1.05–10.32]), defined as the composite of cardiac death, non-fatal MI, clinically driven target vessel revascularization, and re-hospitalization due to unstable or progressive angina at a median follow-up of 10.4 months. Similarly, Vergallo et al. [56] reported that spotty calcifications were more frequent in patients with recurrent ACS than in those with single acute MI and long-standing stable angina.

About CN in a sub-analysis of the CLIMA study, Prati et al. demonstrated that the presence of CN with disruption of the superficial intimal fibrous layer in untreated proximal LAD lesions was a strong independent predictor of future events (composite of cardiac death and target lesion MI) at one-year follow-up (HR 6.58 [95% CI: 2.7–15.8, $p < 0.001$]), whereas overall CN did not predict MACEs in the CLIMA study [8,109]. CN in patients in hemodialysis undergoing PCI were reported to have increased risk of MACEs (HR 4.93 [95% CI: 2.07–11.76]) driven by either all-cause and CV death or target-lesion revascularization at one-year follow-up [110]. Other studies suggested the positive association between CN in different clinical settings (culprit lesion in ACS patients, CN in patients with end-stage renal disease in hemodialysis, and newly developed CN in untreated calcified lesions) and adverse future CV outcomes [111–113].

The relationship between calcifications and CN and negative post-PCI outcomes is well known with either the use of drug-eluting stent, often requiring adequate lesion preparation with specific calcium-modifying devices to reduce the risk of stent underexpansion, or drug-coated balloons, the latter being associated with poor outcomes in calcified lesions and CN, mostly related to increased risk of target lesion revascularization [114–118].

2.8. Previous Ruptures (Cavities Within the Plaque in Stable Patients)

Plaque rupture (PR) is the main pathobiological cause of coronary thrombosis and sudden coronary death in pathology studies [10] and the cause of ACS related to plaque destabilization in intravascular imaging reports [119]. As previously indicated, PR can be recognized at OCT imaging by fibrous cap discontinuity over a lipid-rich necrotic core, typically associated with an intraplaque cavity and superimposed thrombus. Cavities without thrombi can also be identified at the sites of previous plaque rupture or in acute ruptures treated with antithrombotic or thrombolytic therapies [3] (Figure 3C).

Pathology evidence reported that PRs can be found in patients who died for non-cardiac causes without evidence of acute MI [120]. Similarly, three-coronary vessel OCT studies reported non-infarct-related non-culprit PR in about 20% of patients with CAD [104,121]. Plaques with previous rupture at the non-culprit sites were more frequently found in ACS than stable patients, and non-culprit plaques with cavities showed

higher prevalence of TCFA, microvessels, MØI, CCs, calcification, spotty calcifications, and thrombus at the lesion-level than non-culprit lesions without PR [121].

Clinical significance of PR unrelated to acute MI at non-culprit sites has been investigated in few OCT studies [38,121,122]. In a recent OCT patient-data pooled analysis from COMBINE OCT-FFR and PECTUS-obs studies including a total of 810 patients with either acute or chronic coronary artery disease, untreated FFR-negative non-culprit lesions showing plaque rupture had more than 2-fold higher risk of native MACEs (composite of all-cause mortality, nonfatal MI, or unplanned revascularization excluding stent-failure-related events and nonattributable events) and more than 3-fold higher risk of target lesion failure (composite of cardiac death, target vessel MI, or target lesion revascularization) than non-culprit lesions without PR over a median follow-up of about 2 years [122]. Another study showed that patients with non-culprit PR assessed by OCT imaging, of whom only 13% underwent PCI at index OCT, reported higher rates of non-target lesion revascularization (11.8% versus 4.4%; $p = 0.039$) at one-year follow-up, of which two-thirds occurred at sites of non-culprit PR [121]. Conversely, in the study by Xing et al., no differences in non-culprit lesion MACEs were found between non-culprit lesions with and without PR undergoing PCI [38]. Upcoming studies will clarify the significance of previous rupture in the coronary arteries for future events.

3. Therapeutic Implications

Many drugs have shown effects on plaque features as shown by various imaging modalities (OCT, IVUS, coronary computed tomography angiography—CCTA, magnetic resonance imaging, etc.). In the present section, we focused on pharmacological agents with the strongest evidence of plaque structure modification assessed by OCT imaging. We also discuss the potential role of preventive PCI in vulnerable plaques.

3.1. Lipid-Lowering Therapies

Lipid-lowering therapies are the cornerstone of CV prevention and play a central role in reducing LDL cholesterol (LDL-C) levels. Recent evidence showed that these drugs may modify the composition and stability of atherosclerotic plaques. In particular, achieving very low LDL-C levels has been associated with smaller lipid arc, and thicker fibrous caps, and an inverse correlation between LDL-C and fibrous cap thickness has been described [123]. A meta-analysis of 12 randomized control trials also reported a strict correlation between lipid-lowering therapies and thicker fibrous cap and reduced maximum lipid arc [124]. Statins have been the first-line agents since the early 1990s, with consistent evidence from large randomized trials and meta-analyses demonstrating a strong, dose-dependent relationship between LDL-C lowering and reduction in CV events [125]. In addition, statins have been shown to reduce atherosclerotic plaque progression and favor plaque regression by significantly reducing both total atheroma volume (TAV) and percent atheroma volume (PAV) [126–134]. Numerous studies reported that statins act on plaque composition by increasing fibrous and calcified components, by reducing lipid content and necrotic core, and by increasing fibrous cap thickness [135–137]. The YELLOW trial demonstrated a marked reduction in lipid core burden in patients treated with high-dose rosuvastatin [135], while OCT-based studies such as EASY-FIT confirmed increases in fibrous cap thickness and decreases in the grade of OCT-derived macrophages with statin therapy [136]. CCTA analyses, such as in the PARADIGM study, also observed an increase in calcified plaque and a reduction in high-risk features such as positive remodeling [137,138].

Ezetimibe, when added to statin therapy, provides an additional LDL-C reduction and clinical benefit, as demonstrated in the IMPROVE-IT trial [139]. Meta-analyses have further

shown that combination therapy with statins and ezetimibe results in greater plaque volume and TAV reduction compared to statin monotherapy [140,141]. However, the evidence on the impact of ezetimibe on plaque composition is mixed. Some imaging studies, such as those by Hibi et al., found no significant differences in PAV or key plaque features (fibrous, calcified, or lipid content) when ezetimibe was added to statin therapy [142]. Nevertheless, other studies have suggested modest improvements: for instance, Habara et al. reported a significant increase in fibrous cap thickness with fluvastatin-ezetimibe combination therapy versus fluvastatin alone [143]. An OCTIVUS sub-study reported lower prevalence of CCs in patients treated with ezetimibe than placebo [144].

PCSK9 inhibitors, including monoclonal antibodies such as evolocumab and alirocumab, have revolutionized lipid-lowering therapy by enabling profound reductions in LDL-C levels, with a corresponding significant decrease in MACE [145,146]. These agents have also been investigated for their effects on plaque morphology. The GLAGOV trial demonstrated greater reductions in TAV among patients treated with evolocumab compared to statin therapy alone [147], while the ODYSSEY J-IVUS trial, using alirocumab, showed a non-significant trend towards plaque regression [148]. Recent imaging studies using OCT have highlighted the ability of PCSK9 inhibitors to promote plaque stabilization. The HUYGENS trial found that evolocumab significantly increased fibrous cap thickness, reduced maximum lipid arc, and decreased macrophage index throughout arterial segments and LRP regions [149]. Similarly, the PACMAN-AMI trial provided compelling evidence of plaque regression and compositional change in non-culprit coronary arteries of post-acute MI patients treated with alirocumab in addition to high-intensity statins. Compared to statin therapy alone, combination therapy resulted in greater reductions in PAV, lipid burden, and macrophage content, along with a greater increase in fibrous cap thickness [150].

Finally, inclisiran, a small interfering RNA (siRNA) targeting hepatic PCSK9 synthesis, achieves a ~50% LDL-C reduction with twice-yearly subcutaneous administration [151]. Although outcome data from the ORION-4 trial are awaited, there is currently limited evidence on inclisiran effects on plaque composition. The ongoing VICTORION-PLAQUE study is expected to provide further insights into its potential role in plaque stabilization [152].

3.2. Colchicine

Increasing evidence showed that anti-inflammatory therapy represents a new target to fight atherosclerotic disease [153,154]. Colchicine is an anti-inflammatory medication that acts by inhibiting microtubule formation and the polymerization of tubulin, resulting in suppression of the inflammatory response [155]. The LoDoCo2 trial [156] revealed that colchicine reduced the risk of primary composite CV events by 31%, thought to be attributable to its anti-inflammatory effects. In addition, in a recent meta-analysis including 12,869 patients, colchicine therapy was associated with a reduced risk of MI, coronary revascularization, stroke, and hospitalization for CV causes compared to placebo, although no differences emerged for CV and all-cause deaths [157].

Colchicine has shown positive results on modifying plaque composition [158,159]. The COLOCT trial including 128 patients with CAD, reported that patients treated with colchicine had significantly higher minimal fibrous cap thickness, reduced average lipid arc and mean angular extension of macrophages at OCT imaging, as well as lower inflammatory biomarkers, than those treated with placebo at twelve-month follow-up [158]. Finally, the COCOMO-ACS aimed to assess the effect of colchicine post-MI on coronary plaque morphology OCT imaging in non-culprit segments of 64 patients. The study found that there were no differences in minimum FCT and maximum lipid arc throughout the

imaged non-culprit segment, although cap rupture was less frequent. In a post-hoc analysis of patients followed up for 16 months, the increase of minimum FCT was higher in the colchicine than placebo group [159].

3.3. Preventive PCI

Beyond pharmacological strategies aimed at plaque stabilization and regression, several studies have explored, and others are currently investigating, the role of preventive PCI targeting vulnerable or high-risk plaques, as identified by invasive intracoronary imaging or noninvasive modalities.

The first pilot study in this area was the SECRITT trial [160], which randomized 23 patients with non-obstructive vulnerable lesions defined as TCFAs according to VH-IVUS and OCT criteria to PCI with a self-expanding nitinol stent or conservative management. In the PCI group, a substantial decrease in vessel wall strain and a notable increase in fibrous cap thickness were observed at six-month follow-up. Although not powered for clinical events, the SECRITT trial provided a proof-of-concept that plaque treatment with a stent may reduce lipid plaque content and increase cap stability. The PROSPECT-ABSORB was the first large trial comparing a preventive interventional strategy with conservative management of non-obstructing high-risk plaques [161]. Patients with acute MI undergoing PCI of the culprit lesion were screened with IVUS for non-obstructive lesions having plaque burden $\geq$65%. Eligible lesions were randomized to implantation of a coronary bioresorbable vascular scaffold (BVS) or conservative treatment. A total of 182 patients were included (93 in the BVS group and 89 in the conservative group). The primary endpoint—IVUS-derived minimal lumen area—was significantly larger in the PCI group as compared to controls (6.9 ± 2.6 mm^2 vs. 3.0 ± 1.0 mm^2; $p < 0.0001$). However, there were no significant differences in the rate of target lesion failure and MACEs at follow-up, although the study was not powered for clinical events. The first large trial of preventive PCI of vulnerable plaques powered for clinical events was recently published [9]. The PREVENT trial enrolled 1606 patients, mostly presenting with chronic coronary syndromes, being randomized 1:1 to medical treatment or PCI with BVS or drug-eluting stent of vulnerable coronary plaques defined as lesions with angiographic diameter stenosis >50% at angiography and FFR > 0.80, and at least 2 of the following four features: (1) MLA < 4.0 mm^2 by IVUS or OCT; (2) IVUS plaque burden >70%; (3) LRP on near-infrared spectroscopy; (4) TCFA by OCT or radiofrequency-IVUS. The primary outcome was a composite of death from cardiac causes, target-vessel MI, ischemia-driven target-vessel revascularization, or hospitalization for unstable or progressive angina. At 2 years, the primary endpoint occurred in 3.4% of the conservative group and in 0.4% of the interventional group (HR 0.54, 95% CI: 0.33–0.87), suggesting a potential benefit of prophylactic PCI in selected high-risk plaques. However, the PREVENT trial has several notable limitations. Its open-label design may have introduced bias in the reporting of subjective outcomes. Longer duration of dual antiplatelet therapy in the PCI arm could have contributed to the lower event rates, acting as a confounding factor [162,163]. Additionally, the absence of systematic imaging follow-up limits insights into plaque evolution.

4. Future Directions

Many trials using different invasive and noninvasive imaging modalities for plaque assessment are ongoing and will clarify the role of preventive PCI in vulnerable and high-risk plaques. The INTERCLIMA study (NCT05027984) will assess the clinical effectiveness of an OCT-based strategy to guide revascularization in non-culprit intermediate coronary stenosis in patients with acute coronary syndrome (ACS) on the basis of the presence of morphological markers of plaque vulnerability, about a composite of cardiac death

and target vessel spontaneous MI at 2 years and 5 years of follow-up. The COMBINE-INTERVENE study (NCT05333068) will match an OCT-FFR strategy, including OCT plaque assessment vs. FFR alone, in patients with multivessel coronary artery disease candidates for PCI about future MACEs at 24 months. The VULNERABLE trial (NCT05599061) will enroll ST-elevation MI patients with multivessel disease with FFR-negative intermediate lesions showing OCT features of vulnerability and will assess the outcomes related to a PCI with everolimus-eluting stents + optimal medical therapy strategy vs. optimal medical therapy alone about future target vessel failure at 4 years of follow-up. Finally, the FAVOR V trial (NCT05669222) will use noninvasive computerized angiography analysis for lesion functional assessment by quantitative flow ratio (μQFR) and plaque vulnerability evaluation through radial wall strain in ST-segment elevation MI patients with multivessel disease and will compare CCTA-guided PCI vs. coronary angiography +/- invasive functional assessment according to angiographic stenosis-guided PCI about future MACEs at 1.5 years of follow-up. The results of these trials will further clarify the role of preventive PCI in the presence of specific features of plaque vulnerability assessed by imaging about future outcomes.

5. Conclusions

Plaque microstructures identified through intracoronary OCT imaging have shown significant prognostic value in clinical studies. Within the comprehensive assessment of patients with coronary artery disease, such information may help characterize the individual atherosclerotic background and guide the implementation of more effective strategies for secondary prevention. Emerging evidence also suggests that preventive PCI could improve clinical outcomes in selected patients exhibiting high-risk plaque features. Future studies and clinical trials will be crucial to further refine the stratification of both "vulnerable plaques" and "vulnerable patients," ultimately supporting the development of optimized therapeutic approaches aimed at reducing the clinical burden of atherosclerotic CV disease.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm14228132/s1. Table S1: Studies exploring the prognostic impact of OCT-detected microstructures in patients with CAD.

Author Contributions: Conceptualization, M.R. and M.Z.; validation, M.R., E.B., F.R., L.S., F.L.G., A.R., C.V., M.G., S.B., R.V., R.A.M., U.B., G.N., F.P. and M.Z.; investigation, M.R., E.B., F.R. and L.S.; writing—original draft preparation, M.R., E.B., F.R. and L.S.; writing—review and editing, F.L.G., A.R., C.V., M.G., S.B., R.V., R.A.M., U.B., G.N., F.P. and M.Z.; visualization, M.R., E.B., F.R., L.S., F.L.G., A.R., C.V., M.G., S.B., R.V., R.A.M., U.B., G.N., F.P. and M.Z.; supervision, M.R., U.B., G.N., F.P. and M.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: R.V. is a consultant for Abbott Vascular and Medtronic; received lecturing fees from Abbott Vascular, Abiomed, Amgen, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, Johnson & Johnson, Medtronic, Novartis, Novo Nordisk, Penumbra Inc., Philips, and SIS Medical; and served as a member of advisory boards for Amarin, Amgen, and Medtronic. S.B. received lecturing fees from Amgen and Daiichi Sankyo.

References

1. GBD 2021 Forecasting Collaborators. Burden of disease scenarios for 204 countries and territories, 2022–2050: A forecasting analysis for the Global Burden of Disease Study 2021. *Lancet* **2024**, *403*, 2204–2256. [CrossRef] [PubMed] [PubMed Central]

2. Gall, E.; Pezel, T.; Lattuca, B.; Hamzi, K.; Puymirat, E.; Piliero, N.; Deney, A.; Fauvel, C.; Aboyans, V.; Schurtz, G.; et al. Profile of patients hospitalized in intensive cardiac care units in France: ADDICT-ICCU registry. *Arch. Cardiovasc. Dis.* **2024**, *117*, 195–203. [CrossRef] [PubMed]
3. Araki, M.; Park, S.J.; Dauerman, H.L.; Uemura, S.; Kim, J.S.; Di Mario, C.; Johnson, T.W.; Guagliumi, G.; Kastrati, A.; Joner, M.; et al. Optical coherence tomography in coronary atherosclerosis assessment and intervention. *Nat. Rev. Cardiol.* **2022**, *19*, 684–703, Erratum in *Nat. Rev. Cardiol.* **2024**, *21*, 348. [CrossRef] [PubMed] [PubMed Central]
4. Vrints, C.; Andreotti, F.; Koskinas, K.C.; Rossello, X.; Adamo, M.; Ainslie, J.; Banning, A.P.; Budaj, A.; Buechel, R.R.; Chiariello, G.A.; et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur. Heart J.* **2024**, *45*, 3415–3537, Erratum in *Eur. Heart J.* **2025**, *46*, 1565. [CrossRef] [PubMed]
5. Byrne, R.A.; Rossello, X.; Coughlan, J.J.; Barbato, E.; Berry, C.; Chieffo, A.; Claeys, M.J.; Dan, G.A.; Dweck, M.R.; Galbraith, M.; et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur. Heart J.* **2023**, *44*, 3720–3826, Erratum in *Eur. Heart J.* **2024**, *45*, 1145. [CrossRef] [PubMed]
6. Prati, F.; Guagliumi, G.; Mintz, G.S.; Costa, M.; Regar, E.; Akasaka, T.; Barlis, P.; Tearney, G.J.; Jang, I.K.; Arbustini, E.; et al. Expert review document part 2: Methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. *Eur. Heart J.* **2012**, *33*, 2513–2520. [CrossRef] [PubMed] [PubMed Central]
7. Johnson, T.W.; Räber, L.; di Mario, C.; Bourantas, C.; Jia, H.; Mattesini, A.; Gonzalo, N.; de la Torre Hernandez, J.M.; Prati, F.; Koskinas, K.; et al. Clinical use of intracoronary imaging. Part 2: Acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur. Heart J.* **2019**, *40*, 2566–2584. [CrossRef] [PubMed]
8. Prati, F.; Romagnoli, E.; Gatto, L.; La Manna, A.; Burzotta, F.; Ozaki, Y.; Marco, V.; Boi, A.; Fineschi, M.; Fabbiocchi, F.; 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*, 383–391, Erratum in *Eur. Heart J.* **2020**, *41*, 393. [CrossRef] [PubMed]
9. Park, S.J.; Ahn, J.M.; Kang, D.Y.; Yun, S.C.; Ahn, Y.K.; Kim, W.J.; Nam, C.W.; Jeong, J.O.; Chae, I.H.; Shiomi, H.; et al. Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): A multicentre, open-label, randomised controlled trial. *Lancet* **2024**, *403*, 1753–1765, Erratum in *Lancet* **2024**, *404*, 1928. [CrossRef] [PubMed]
10. Virmani, R.; Burke, A.P.; Farb, A.; Kolodgie, F.D. Pathology of the vulnerable plaque. *J. Am. Coll. Cardiol.* **2006**, *47* (Suppl. 8), C13–C18. [CrossRef] [PubMed]
11. Otsuka, F.; Yasuda, S.; Noguchi, T.; Ishibashi-Ueda, H. Pathology of coronary atherosclerosis and thrombosis. *Cardiovasc. Diagn. Ther.* **2016**, *6*, 396–408. [CrossRef] [PubMed] [PubMed Central]
12. Gurgoglione, F.L.; Denegri, A.; Russo, M.; Calvieri, C.; Benatti, G.; Niccoli, G. Intracoronary Imaging of Coronary Atherosclerotic Plaque: From Assessment of Pathophysiological Mechanisms to Therapeutic Implication. *Int. J. Mol. Sci.* **2023**, *24*, 5155. [CrossRef] [PubMed] [PubMed Central]
13. Burke, A.P.; Farb, A.; Malcom, G.T.; Liang, Y.H.; Smialek, J.; Virmani, R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N. Engl. J. Med.* **1997**, *336*, 1276–1282. [CrossRef] [PubMed]
14. Araki, M.; Soeda, T.; Kim, H.O.; Thondapu, V.; Russo, M.; Kurihara, O.; Shinohara, H.; Minami, Y.; Higuma, T.; Lee, H.; et al. Spatial Distribution of Vulnerable Plaques: Comprehensive In Vivo Coronary Plaque Mapping. *JACC Cardiovasc. Imaging* **2020**, *13*, 1989–1999. [CrossRef] [PubMed]
15. Iannaccone, M.; Quadri, G.; Taha, S.; D'Ascenzo, F.; Montefusco, A.; Omede', P.; Jang, I.K.; Niccoli, G.; Souteyrand, G.; Yundai, C.; et al. Prevalence and predictors of culprit plaque rupture at OCT in patients with coronary artery disease: A meta-analysis. *Eur. Heart J. Cardiovasc. Imaging* **2016**, *17*, 1128–1137. [CrossRef] [PubMed]
16. Raffel, O.C.; Tearney, G.J.; Gauthier, D.D.; Halpern, E.F.; Bouma, B.E.; Jang, I.K. Relationship between a systemic inflammatory marker, plaque inflammation, and plaque characteristics determined by intravascular optical coherence tomography. *Arterioscler. Thromb. Vasc. Biol.* **2007**, *27*, 1820–1827. [CrossRef] [PubMed] [PubMed Central]
17. Aguirre, A.D.; Arbab-Zadeh, A.; Soeda, T.; Fuster, V.; Jang, I.K. Optical Coherence Tomography of Plaque Vulnerability and Rupture: JACC Focus Seminar Part 1/3. *J. Am. Coll. Cardiol.* **2021**, *78*, 1257–1265. [CrossRef] [PubMed] [PubMed Central]
18. Xue, C.; Chen, Q.; Bian, L.; Yin, Z.; Xu, Z.; Zhang, H.; Zhang, Q.; Zhang, J.; Wang, C.; Du, R.; et al. The relationships between cholesterol crystals, NLRP3 inflammasome, and coronary atherosclerotic plaque vulnerability in acute coronary syndrome: An optical coherence tomography study. *Front. Cardiovasc. Med.* **2022**, *9*, 905363. [CrossRef] [PubMed] [PubMed Central]
19. Yang, C.; Deng, C.; Xia, J.; Wang, S.; Zhang, L.; Liu, Z.; Zhang, W.; Deng, Y.; Lu, S.; Xu, G.; et al. Peri-coronary adipose tissue attenuation and its association with plaque vulnerability and clinical outcomes in coronary artery disease using combined CCTA and OCT. *Sci. Rep.* **2025**, *15*, 16520. [CrossRef] [PubMed] [PubMed Central]
20. Katamine, M.; Minami, Y.; Nagata, T.; Asakura, K.; Muramatsu, Y.; Kinoshita, D.; Fujiyoshi, K.; Ako, J. High-sensitivity C-reactive protein, plaque vulnerability and adverse events in patients with stable coronary disease: An optical coherence tomography study. *Int. J. Cardiol.* **2025**, *421*, 132924. [CrossRef] [PubMed]

21. Dai, J.; Zhao, J.; Xu, X.; Chen, Y.; Sun, S.; Li, S.; Cui, L.; Wang, Y.; Li, L.; Guo, R.; et al. Long-Term Prognostic Implications of Non-Culprit Lesions in Patients Presenting with an Acute Myocardial Infarction: Is It the Angiographic Stenosis Severity or the Underlying High-Risk Morphology? *Circulation* **2025**, *151*, 1098–1110. [CrossRef] [PubMed]
22. Biccirè, F.G.; Fabbiocchi, F.; Gatto, L.; La Manna, A.; Ozaki, Y.; Romagnoli, E.; Marco, V.; Boi, A.; Fineschi, M.; Piedimonte, G.; et al. Long-Term Prognostic Impact of OCT-Derived High-Risk Plaque Features: Extended Follow-Up of the CLIMA Study. *JACC Cardiovasc. Interv.* **2025**, *18*, 1361–1372. [CrossRef] [PubMed]
23. Fabris, E.; Berta, B.; Hommels, T.; Roleder, T.; Hermanides, R.S.; Rivero, F.; von Birgelen, C.; Escaned, J.; Camaro, C.; Kennedy, M.W.; et al. Long-term outcomes of patients with normal fractional flow reserve and thin-cap fibroatheroma. *EuroIntervention* **2023**, *18*, e1099–e1107. [CrossRef] [PubMed] [PubMed Central]
24. Gallone, G.; Bellettini, M.; Gatti, M.; Tore, D.; Bruno, F.; Scudeler, L.; Cusenza, V.; Lanfranchi, A.; Angelini, A.; de Filippo, O.; et al. Coronary Plaque Characteristics Associated with Major Adverse Cardiovascular Events in Atherosclerotic Patients and Lesions: A Systematic Review and Meta-Analysis. *JACC Cardiovasc. Imaging* **2023**, *16*, 1584–1604, Erratum in *JACC Cardiovasc. Imaging* **2024**, *17*, 578. [CrossRef] [PubMed]
25. Jiang, S.; Fang, C.; Xu, X.; Xing, L.; Sun, S.; Peng, C.; Yin, Y.; Lei, F.; Wang, Y.; Li, L.; et al. Identification of High-Risk Coronary Lesions by 3-Vessel Optical Coherence Tomography. *J. Am. Coll. Cardiol.* **2023**, *81*, 1217–1230. [CrossRef] [PubMed]
26. Kubo, T.; Ino, Y.; Mintz, G.S.; Shiono, Y.; Shimamura, K.; Takahata, M.; Terada, K.; Higashioka, D.; Emori, H.; Wada, T.; et al. Optical coherence tomography detection of vulnerable plaques at high risk of developing acute coronary syndrome. *Eur. Heart J. Cardiovasc. Imaging* **2021**, *22*, 1376–1384. [CrossRef] [PubMed]
27. Yamaji, K.; Kanenawa, K.; Morofuji, T.; Nishikawa, R.; Imada, K.; Kohjitani, H.; Watanabe, H.; Tazaki, J.; Taniwaki, M.; Koga, S.; et al. Serial Optical Coherence Tomography Assessment of Coronary Atherosclerosis and Long-Term Clinical Outcomes. *J. Am. Heart Assoc.* **2024**, *13*, e034458. [CrossRef] [PubMed] [PubMed Central]
28. Kedhi, E.; Berta, B.; Roleder, T.; Hermanides, R.S.; Fabris, E.; IJsselmuiden, A.J.J.; Kauer, F.; Alfonso, F.; von Birgelen, C.; Escaned, J.; 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*, 4671–4679. [CrossRef] [PubMed]
29. Russo, M.; Fracassi, F.; Kurihara, O.; Kim, H.O.; Thondapu, V.; Araki, M.; Shinohara, H.; Sugiyama, T.; Yamamoto, E.; Lee, H.; et al. Healed Plaques in Patients With Stable Angina Pectoris. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 1587–1597. [CrossRef] [PubMed]
30. Vergallo, R.; Crea, F. Atherosclerotic Plaque Healing. *N. Engl. J. Med.* **2020**, *383*, 846–857. [CrossRef] [PubMed]
31. Araki, M.; Yonetsu, T.; Kurihara, O.; Nakajima, A.; Lee, H.; Soeda, T.; Minami, Y.; McNulty, I.; Uemura, S.; Kakuta, T.; et al. Predictors of Rapid Plaque Progression: An Optical Coherence Tomography Study. *JACC Cardiovasc. Imaging* **2021**, *14*, 1628–1638. [CrossRef] [PubMed]
32. Xu, Y.; Ma, J.; He, L.; Zhang, D.; Yi, B.; Zuo, Y.; Qin, Y.; Zhao, C.; Weng, Z.; Sun, Y.; et al. Predictors and Mechanisms of Nonculprit Plaque Progression in Patients With Acute Coronary Syndromes: An In-Vivo Serial Optical Coherence Tomography Study. *Am. J. Cardiol.* **2025**, *249*, 19–28. [CrossRef] [PubMed]
33. Russo, M.; Kim, H.O.; Kurihara, O.; Araki, M.; Shinohara, H.; Thondapu, V.; Yonetsu, T.; Soeda, T.; Minami, Y.; Higuma, T.; et al. Characteristics of non-culprit plaques in acute coronary syndrome patients with layered culprit plaque. *Eur. Heart J. Cardiovasc. Imaging* **2020**, *21*, 1421–1430. [CrossRef] [PubMed]
34. Sibbald, M.; Pinilla-Echeverri, N.; Alameer, M.; Chavarria, J.; Dutra, G.; Sheth, T. Using Optical Coherence Tomography to Identify Lipid and Its Impact on Interventions and Clinical Events—A Scoping Review. *Circ. J.* **2021**, *85*, 2053–2062. [CrossRef] [PubMed]
35. Kato, K.; Yonetsu, T.; Kim, S.J.; Xing, L.; Lee, H.; McNulty, I.; Yeh, R.W.; Sakhuja, R.; Zhang, S.; Uemura, S.; et al. Nonculprit plaques in patients with acute coronary syndromes have more vulnerable features compared with those with non-acute coronary syndromes: A 3-vessel optical coherence tomography study. *Circ. Cardiovasc. Imaging* **2012**, *5*, 433–440. [CrossRef] [PubMed]
36. Di Vito, L.; Agozzino, M.; Marco, V.; Ricciardi, A.; Concardi, M.; Romagnoli, E.; Gatto, L.; Calogero, G.; Tavazzi, L.; Arbustini, E.; et al. Identification and quantification of macrophage presence in coronary atherosclerotic plaques by optical coherence tomography. *Eur. Heart J. Cardiovasc. Imaging* **2015**, *16*, 807–813. [CrossRef] [PubMed]
37. Nakajima, A.; Araki, M.; Kurihara, O.; Minami, Y.; Soeda, T.; Yonetsu, T.; Higuma, T.; Kakuta, T.; McNulty, I.; Lee, H.; et al. Predictors for Rapid Progression of Coronary Calcification: An Optical Coherence Tomography Study. *J. Am. Heart Assoc.* **2021**, *10*, e019235. [CrossRef] [PubMed] [PubMed Central]
38. Xing, L.; Higuma, T.; Wang, Z.; Aguirre, A.D.; Mizuno, K.; Takano, M.; Dauerman, H.L.; Park, S.J.; Jang, Y.; Kim, C.J.; 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*, 2502–2513. [CrossRef] [PubMed]
39. Biccirè, F.G.; Budassi, S.; Ozaki, Y.; Boi, A.; Romagnoli, E.; Di Pietro, R.; Bourantas, C.V.; Marco, V.; Paoletti, G.; Debelak, C.; et al. Optical coherence tomography-derived lipid core burden index and clinical outcomes: Results from the CLIMA registry. *Eur. Heart J. Cardiovasc. Imaging* **2023**, *24*, 437–445. [CrossRef] [PubMed]

40. Fabris, E.; Berta, B.; Roleder, T.; Hermanides, R.S.; IJsselmuiden, A.J.J.; Kauer, F.; Alfonso, F.; von Birgelen, C.; Escaned, J.; Camaro, C.; et al. Thin-Cap Fibroatheroma Rather than Any Lipid Plaques Increases the Risk of Cardiovascular Events in Diabetic Patients: Insights From the COMBINE OCT-FFR Trial. *Circ. Cardiovasc. Interv.* **2022**, *15*, e011728. [CrossRef] [PubMed]
41. Shimokado, A.; Matsuo, Y.; Kubo, T.; Nishiguchi, T.; Taruya, A.; Teraguchi, I.; Shiono, Y.; Orii, M.; Tanimoto, T.; Yamano, T.; et al. In vivo optical coherence tomography imaging and histopathology of healed coronary plaques. *Atherosclerosis* **2018**, *275*, 35–42. [CrossRef] [PubMed]
42. Russo, M.; Rinaldi, R.; Camilli, M.; Bonanni, A.; Caffè, A.; Basile, M.; Salzillo, C.; Colucci, M.; Torre, I.; Sanna, T.; et al. Air pollution and plaque healing in acute coronary syndromes. *Eur. Heart J.* **2023**, *44*, 2403–2405. [CrossRef] [PubMed]
43. Burke, A.P.; Kolodgie, F.D.; Farb, A.; Weber, D.K.; Malcom, G.T.; Smialek, J.; Virmani, R. Healed plaque ruptures and sudden coronary death: Evidence that subclinical rupture has a role in plaque progression. *Circulation* **2001**, *103*, 934–940. [CrossRef]
44. Mann, J.; Davies, M.J. Mechanisms of progression in native coronary artery disease: Role of healed plaque disruption. *Heart* **1999**, *82*, 265–268. [CrossRef]
45. Yamamoto, M.H.; Yamashita, K.; Matsumura, M.; Fujino, A.; Ishida, M.; Ebara, S.; Okabe, T.; Saito, S.; Hoshimoto, K.; Amemiya, K.; et al. Serial 3-vessel optical coherence tomography and intravascular ultrasound analysis of changing morphologies associated with lesion progression in patients with stable angina pectoris. *Circ. Cardiovasc. Imaging* **2017**, *10*, e006347. [CrossRef]
46. Araki, M.; Yonetsu, T.; Russo, M.; Kurihara, O.; Kim, H.O.; Shinohara, H.; Thondapu, V.; Soeda, T.; Minami, Y.; Higuma, T.; et al. Predictors for layered coronary plaques: An optical coherence tomography study. *J. Thromb. Thrombolysis* **2020**, *50*, 886–894. [CrossRef] [PubMed]
47. Kurihara, O.; Russo, M.; Kim, H.O.; Araki, M.; Shinohara, H.; Lee, H.; Takano, M.; Mizuno, K.; Jang, I.K. Clinical significance of healed plaque detected by optical coherence tomography: A 2-year follow-up study. *J. Thromb. Thrombolysis* **2020**, *50*, 895–902. [CrossRef] [PubMed]
48. Yi, B.; He, L.; Zhang, D.; Zeng, M.; Zhao, C.; Meng, W.; Qin, Y.; Weng, Z.; Xu, Y.; Liu, M.; et al. Non-culprit plaque healing on serial OCT imaging and future outcome in patients with acute coronary syndromes. *Atherosclerosis* **2025**, *401*, 119092. [CrossRef] [PubMed]
49. Usui, E.; Mintz, G.S.; Lee, T.; Matsumura, M.; Zhang, Y.; Hada, M.; Yamaguchi, M.; Hoshino, M.; Kanaji, Y.; Sugiyama, T.; et al. Prognostic impact of healed coronary plaque in non-culprit lesions assessed by optical coherence tomography. *Atherosclerosis* **2020**, *309*, 1–7. [CrossRef] [PubMed]
50. Del Val, D.; Berta, B.; Roleder, T.; Malinowski, K.; Bastante, T.; Hermanides, R.S.; Wojakowski, W.; Fabris, E.; Cuesta, J.; De Luca, G.; et al. Vulnerable plaque features and adverse events in patients with diabetes mellitus: A post hoc analysis of the COMBINE OCT-FFR trial. *EuroIntervention* **2024**, *20*, e707–e717. [CrossRef] [PubMed]
51. Kimura, S.; Isshiki, A.; Shimizu, M.; Fujii, H.; Suzuki, M. Clinical Significance of Coronary Healed Plaques in Stable Angina Pectoris Patients Undergoing Percutaneous Coronary Intervention. *Circ. J.* **2023**, *87*, 1643–1653. [CrossRef] [PubMed]
52. Fracassi, F.; Crea, F.; Sugiyama, T.; Yamamoto, E.; Uemura, S.; Vergallo, R.; Porto, I.; Lee, H.; Fujimoto, J.; Fuster, V.; et al. Healed Culprit Plaques in Patients with Acute Coronary Syndromes. *J. Am. Coll. Cardiol.* **2019**, *73*, 2253–2263. [CrossRef] [PubMed]
53. Yin, Y.; Fang, C.; Jiang, S.; Wang, J.; Wang, Y.; Guo, J.; Lei, F.; Sun, S.; Pei, X.; Jia, R.; et al. In vivo evidence of atherosclerotic plaque erosion and healing in patients with acute coronary syndrome using serial optical coherence tomography imaging. *Am. Heart J.* **2022**, *243*, 66–76. [CrossRef] [PubMed]
54. Dai, J.; Fang, C.; Zhang, S.; Li, L.; Wang, Y.; Xing, L.; Yu, H.; Jiang, S.; Yin, Y.; Wang, J.; et al. Frequency, Predictors, Distribution, and Morphological Characteristics of Layered Culprit and Nonculprit Plaques of Patients with Acute Myocardial Infarction: In Vivo 3-Vessel Optical Coherence Tomography Study. *Circ. Cardiovasc. Interv.* **2020**, *13*, e009125. [CrossRef] [PubMed]
55. Wang, C.; Hu, S.; Wu, J.; Yu, H.; Pan, W.; Qin, Y.; He, L.; Li, L.; Hou, J.; Zhang, S.; et al. Characteristics and significance of healed plaques in patients with acute coronary syndrome and stable angina: An in vivo OCT and IVUS study. *EuroIntervention* **2019**, *15*, e771–e778. [CrossRef] [PubMed]
56. Vergallo, R.; Porto, I.; D'Amario, D.; Annibali, G.; Galli, M.; Benenati, S.; Bendandi, F.; Migliaro, S.; Fracassi, F.; Aurigemma, C.; et al. Coronary Atherosclerotic Phenotype and Plaque Healing in Patients with Recurrent Acute Coronary Syndromes Compared with Patients with Long-term Clinical Stability: An In Vivo Optical Coherence Tomography Study. *JAMA Cardiol.* **2019**, *4*, 321–329. [CrossRef] [PubMed] [PubMed Central]
57. Kurihara, O.; Shinohara, H.; Kim, H.O.; Russo, M.; Araki, M.; Nakajima, A.; Lee, H.; Takano, M.; Mizuno, K.; Komuro, I.; et al. Comparison of post-stent optical coherence tomography findings: Layered versus non-layered culprit lesions. *Catheter. Cardiovasc. Interv.* **2021**, *97*, 1320–1328. [CrossRef] [PubMed]
58. Tearney, G.J.; Yabushita, H.; Houser, S.L.; Aretz, H.T.; Jang, I.K.; Schlendorf, K.H.; Kauffman, C.R.; Shishkov, M.; Halpern, E.F.; Bouma, B.E. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation* **2003**, *107*, 113–119. [CrossRef] [PubMed]

59. Phipps, J.E.; Vela, D.; Hoyt, T.; Halaney, D.L.; Mancuso, J.J.; Buja, L.M.; Asmis, R.; Milner, T.E.; Feldman, M.D. Macrophages and intravascular OCT bright spots: A quantitative study. *JACC Cardiovasc. Imaging* **2015**, *8*, 63–72. [CrossRef] [PubMed] [PubMed Central]
60. Minami, Y.; Phipps, J.E.; Hoyt, T.; Milner, T.E.; Ong, D.S.; Soeda, T.; Vergallo, R.; Feldman, M.D.; Jang, I.K. Clinical utility of quantitative bright spots analysis in patients with acute coronary syndrome: An optical coherence tomography study. *Int. J. Cardiovasc. Imaging* **2015**, *31*, 1479–1487. [CrossRef] [PubMed]
61. Liu, C.; Yang, F.; Hu, Y.; Wang, L.; Li, X.; Cong, H.; Zhang, J. The relationships between inflammatory biomarkers, plaque characteristics, and macrophage clusters in coronary plaque: A quantitative assessment of macrophages based on optical coherence tomography. *Front. Cardiovasc. Med.* **2025**, *12*, 1625239. [CrossRef] [PubMed] [PubMed Central]
62. Rico-Jimenez, J.J.; Campos-Delgado, D.U.; Buja, L.M.; Vela, D.; Jo, J.A. Intravascular optical coherence tomography method for automated detection of macrophage infiltration within atherosclerotic coronary plaques. *Atherosclerosis* **2019**, *290*, 94–102. [CrossRef] [PubMed] [PubMed Central]
63. MacNeill, B.D.; Jang, I.K.; Bouma, B.E.; Iftimia, N.; Takano, M.; Yabushita, H.; Shishkov, M.; Kauffman, C.R.; Houser, S.L.; Aretz, H.T.; et al. Focal and multi-focal plaque macrophage distributions in patients with acute and stable presentations of coronary artery disease. *J. Am. Coll. Cardiol.* **2004**, *44*, 972–979. [CrossRef] [PubMed]
64. Scalone, G.; Niccoli, G.; Refaat, H.; Vergallo, R.; Porto, I.; Leone, A.M.; Burzotta, F.; D'Amario, D.; Liuzzo, G.; Fracassi, F.; et al. Not all plaque ruptures are born equal: An optical coherence tomography study. *Eur. Heart J. Cardiovasc. Imaging* **2017**, *18*, 1271–1277. [CrossRef] [PubMed]
65. Yuki, H.; Sugiyama, T.; Suzuki, K.; Kinoshita, D.; Niida, T.; Nakajima, A.; Araki, M.; Dey, D.; Lee, H.; McNulty, I.; et al. Coronary Inflammation and Plaque Vulnerability: A Coronary Computed Tomography and Optical Coherence Tomography Study. *Circ. Cardiovasc. Imaging* **2023**, *16*, e014959. [CrossRef] [PubMed]
66. Gatto, L.; Alfonso, F.; Paoletti, G.; Burzotta, F.; La Manna, A.; Budassi, S.; Biccirè, F.G.; Fineschi, M.; Marco, V.; Fabbiocchi, F.; et al. Relationship betweeen the amount and location of macrophages and clinical outcome: Subanalysis of the CLIMA-study. *Int. J. Cardiol.* **2022**, *346*, 8–12. [CrossRef] [PubMed]
67. Iannaccone, M.; Souteyrand, G.; Niccoli, G.; Mancone, M.; Sardella, G.; Tamburino, C.; Templin, C.; Gili, S.; Boccuzzi, G.G.; D'Ascenzo, F. Clinical impact of optical coherence tomography findings on culprit plaque in acute coronary syndrome: The OCT-FORMIDABLE study registry. *Catheter. Cardiovasc. Interv.* **2018**, *92*, E486–E492. [CrossRef] [PubMed]
68. Burgmaier, M.; Milzi, A.; Dettori, R.; Burgmaier, K.; Hellmich, M.; Almalla, M.; Marx, N.; Reith, S. Colocalization of plaque macrophages and calcification in coronary plaques as detected by optical coherence tomography predicts cardiovascular outcome. *Cardiol. J.* **2020**, *27*, 303–306. [CrossRef] [PubMed] [PubMed Central]
69. Fracassi, F.; Niccoli, G.; Vetrugno, V.; Russo, M.; Rettura, F.; Vergni, F.; Scalone, G.; Montone, R.A.; Vergallo, R.; D'Amario, D.; et al. Optical coherence tomography and C-reactive protein in risk stratification of acute coronary syndromes. *Int. J. Cardiol.* **2019**, *286*, 7–12. [CrossRef] [PubMed]
70. Montone, R.A.; Vetrugno, V.; Camilli, M.; Russo, M.; Fracassi, F.; Khan, S.Q.; Doshi, S.N.; Townend, J.N.; Ludman, P.F.; Trani, C.; et al. Macrophage infiltrates in coronary plaque erosion and cardiovascular outcome in patients with acute coronary syndrome. *Atherosclerosis* **2020**, *311*, 158–166. [CrossRef] [PubMed]
71. Russo, M.; Jang, I.K. Cholesterol crystals in atherosclerotic plaques: A future target to reduce the risk of plaque rupture? *Int. J. Cardiol.* **2022**, *365*, 30–31. [CrossRef] [PubMed]
72. Abela, G.S.; Aziz, K.; Vedre, A.; Pathak, D.R.; Talbott, J.D.; Dejong, J. Effect of cholesterol crystals on plaques and intima in arteries of patients with acute coronary and cerebrovascular syndromes. *Am. J. Cardiol.* **2009**, *103*, 959–968. [CrossRef] [PubMed]
73. Nidorf, S.M.; Fiolet, A.; Abela, G.S. Viewing atherosclerosis through a crystal lens: How the evolving structure of cholesterol crystals in atherosclerotic plaque alters its stability. *J. Clin. Lipidol.* **2020**, *14*, 619–630. [CrossRef]
74. Jinnouchi, H.; Sato, Y.; Torii, S.; Sakamoto, A.; Cornelissen, A.; Bhoite, R.R.; Kuntz, S.; Guo, L.; Paek, K.H.; Fernandez, R.; et al. Detection of cholesterol crystals by optical coherence tomography. *EuroIntervention* **2020**, *16*, 395–403. [CrossRef] [PubMed]
75. Katayama, Y.; Tanaka, A.; Taruya, A.; Kashiwagi, M.; Nishiguchi, T.; Ozaki, Y.; Matsuo, Y.; Kitabata, H.; Kubo, T.; Shimada, E.; et al. Feasibility and Clinical Significance of In Vivo Cholesterol Crystal Detection Using Optical Coherence Tomography. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 220–229. [CrossRef] [PubMed]
76. Deng, C.; Liu, Z.; Li, C.; Xu, G.; Zhang, R.; Bai, Z.; Hu, X.; Xia, Q.; Pan, L.; Wang, S.; et al. Predictive models for cholesterol crystals and plaque vulnerability in acute myocardial infarction: Insights from an optical coherence tomography study. *Int. J. Cardiol.* **2025**, *418*, 132610. [CrossRef] [PubMed]
77. Qin, Z.; Cao, M.; Xi, X.; Zhang, Y.; Wang, Z.; Zhao, S.; Tian, Y.; Xu, Q.; Yu, H.; Tian, J.; et al. Cholesterol crystals in non-culprit plaques of STEMI patients: A 3-vessel OCT study. *Int. J. Cardiol.* **2022**, *364*, 162–168. [CrossRef] [PubMed]
78. Nishimura, S.; Ehara, S.; Hasegawa, T.; Matsumoto, K.; Yoshikawa, J.; Shimada, K. Cholesterol crystal as a new feature of coronary vulnerable plaques: An optical coherence tomography study. *J. Cardiol.* **2017**, *69*, 253–259. [CrossRef] [PubMed]

79. Fujiyoshi, K.; Minami, Y.; Ishida, K.; Kato, A.; Katsura, A.; Muramatsu, Y.; Sato, T.; Kakizaki, R.; Nemoto, T.; Hashimoto, T.; et al. Incidence, factors, and clinical significance of cholesterol crystals in coronary plaque: An optical coherence tomography study. *Atherosclerosis* **2019**, *283*, 79–84. [CrossRef] [PubMed]
80. Nelles, G.; Abdelwahed, Y.S.; Seppelt, C.; Meteva, D.; Stähli, B.E.; Rai, H.; Seegers, L.M.; Sieronski, L.; Musfeldt, J.; Gerhardt, T.; et al. Cholesterol crystals at the culprit lesion in patients with acute coronary syndrome are associated with worse cardiovascular outcomes at two years follow up—Results from the translational OPTICO-ACS study program. *Int. J. Cardiol.* **2024**, *399*, 131665. [CrossRef] [PubMed]
81. Usui, E.; Matsumura, M.; Mintz, G.S.; Zhou, Z.; Hada, M.; Yamaguchi, M.; Hoshino, M.; Kanaji, Y.; Sugiyama, T.; Murai, T.; et al. Clinical outcomes of low-intensity area without attenuation and cholesterol crystals in non-culprit lesions assessed by optical coherence tomography. *Atherosclerosis* **2021**, *332*, 41–47. [CrossRef] [PubMed]
82. Bentzon, J.F.; Otsuka, F.; Virmani, R.; Falk, E. Mechanisms of plaque formation and rupture. *Circ. Res.* **2014**, *114*, 1852–1866. [CrossRef] [PubMed]
83. Moreno, P.R.; Purushothaman, K.R.; Fuster, V.; Echeverri, D.; Truszczynska, H.; Sharma, S.K.; Badimon, J.J.; O'Connor, W.N. Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta: Implications for plaque vulnerability. *Circulation* **2004**, *110*, 2032–2038. [CrossRef] [PubMed]
84. Kume, T.; Okura, H.; Yamada, R.; Koyama, T.; Fukuhara, K.; Kawamura, A.; Imai, K.; Neishi, Y.; Uemura, S. Detection of Plaque Neovascularization by Optical Coherence Tomography: Ex Vivo Feasibility Study and In Vivo Observation in Patients with Angina Pectoris. *J. Invasive Cardiol.* **2016**, *28*, 17–22. [PubMed]
85. Aoki, T.; Rodriguez-Porcel, M.; Matsuo, Y.; Cassar, A.; Kwon, T.G.; Franchi, F.; Gulati, R.; Kushwaha, S.S.; Lennon, R.J.; Lerman, L.O.; et al. Evaluation of coronary adventitial vasa vasorum using 3D optical coherence tomography–animal and human studies. *Atherosclerosis* **2015**, *239*, 203–208. [CrossRef] [PubMed] [PubMed Central]
86. Kitabata, H.; Tanaka, A.; Kubo, T.; Takarada, S.; Kashiwagi, M.; Tsujioka, H.; Ikejima, H.; Kuroi, A.; Kataiwa, H.; Ishibashi, K.; et al. Relation of microchannel structure identified by optical coherence tomography to plaque vulnerability in patients with coronary artery disease. *Am. J. Cardiol.* **2010**, *105*, 1673–1678. [CrossRef] [PubMed]
87. Amano, H.; Koizumi, M.; Okubo, R.; Yabe, T.; Watanabe, I.; Saito, D.; Toda, M.; Ikeda, T. Comparison of Coronary Intimal Plaques by Optical Coherence Tomography in Arteries With Versus Without Internal Running Vasa Vasorum. *Am. J. Cardiol.* **2017**, *119*, 1512–1517. [CrossRef] [PubMed]
88. Uemura, S.; Ishigami, K.; Soeda, T.; Okayama, S.; Sung, J.H.; Nakagawa, H.; Somekawa, S.; Takeda, Y.; Kawata, H.; Horii, M.; et al. Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. *Eur. Heart J.* **2012**, *33*, 78–85. [CrossRef] [PubMed]
89. Takeshige, R.; Otake, H.; Kawamori, H.; Toba, T.; Nagano, Y.; Tsukiyama, Y.; Yanaka, K.I.; Yamamoto, H.; Nagasawa, A.; Onishi, H.; et al. Progression from normal vessel wall to atherosclerotic plaque: Lessons from an optical coherence tomography study with follow-up of over 5 years. *Heart Vessel.* **2022**, *37*, 1–11. [CrossRef] [PubMed]
90. Sakamoto, A.; Suwa, K.; Kawakami, R.; Finn, A.V.; Maekawa, Y.; Virmani, R.; Finn, A.V. Significance of Intra-plaque Hemorrhage for the Development of High-Risk Vulnerable Plaque: Current Understanding from Basic to Clinical Points of View. *Int. J. Mol. Sci.* **2023**, *24*, 13298. [CrossRef] [PubMed] [PubMed Central]
91. Xu, T.; Lin, L.; Chen, M.; Zhang, J.J.; Ye, F.; Pan, T.; Huang, X.; Chen, S.L. Coronary Artery Intraplaque Microvessels by Optical Coherence Tomography Correlate with Vulnerable Plaque and Predict Clinical Outcomes in Patients with Ischemic Angina. *JACC Cardiovasc. Interv.* **2018**, *11*, 1421–1422. [CrossRef] [PubMed]
92. Waring, O.J.; Skenteris, N.T.; Biessen, E.A.L.; Donners, M.M.P.C. Two-faced Janus: The dual role of macrophages in atherosclerotic calcification. *Cardiovasc. Res.* **2022**, *118*, 2768–2777. [CrossRef] [PubMed] [PubMed Central]
93. Yabushita, H.; Bouma, B.E.; Houser, S.L.; Aretz, H.T.; Jang, I.K.; Schlendorf, K.H.; Kauffman, C.R.; Shishkov, M.; Kang, D.H.; Halpern, E.F.; et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation* **2002**, *106*, 1640–1645. [CrossRef] [PubMed]
94. Liu, C.; Yang, F.; Hu, Y.; Wang, L.; Li, X.; Cong, H.; Zhang, J. Relationship between coronary artery calcification and plaque vulnerability, a qualitative and quantitative optical coherence tomography study. *Int. J. Cardiol.* **2025**, *440*, 133707. [CrossRef] [PubMed]
95. Fujimoto, D.; Kinoshita, D.; Suzuki, K.; Niida, T.; Yuki, H.; McNulty, I.; Lee, H.; Otake, H.; Shite, J.; Ferencik, M.; et al. Relationship Between Calcified Plaque Burden, Vascular Inflammation, and Plaque Vulnerability in Patients with Coronary Atherosclerosis. *JACC Cardiovasc. Imaging* **2024**, *17*, 1214–1224. [CrossRef] [PubMed]
96. Sugiyama, T.; Yamamoto, E.; Fracassi, F.; Lee, H.; Yonetsu, T.; Kakuta, T.; Soeda, T.; Saito, Y.; Yan, B.P.; Kurihara, O.; et al. Calcified Plaques in Patients With Acute Coronary Syndromes. *JACC Cardiovasc. Interv.* **2019**, *12*, 531–540. [CrossRef] [PubMed]
97. Mauriello, A.; Servadei, F.; Zoccai, G.B.; Giacobbi, E.; Anemona, L.; Bonanno, E.; Casella, S. Coronary calcification identifies the vulnerable patient rather than the vulnerable Plaque. *Atherosclerosis* **2013**, *229*, 124–129. [CrossRef] [PubMed]

98. Grandhi, G.R.; Mszar, R.; Cainzos-Achirica, M.; Rajan, T.; Latif, M.A.; Bittencourt, M.S.; Shaw, L.J.; Batlle, J.C.; Blankstein, R.; Blaha, M.J.; et al. Coronary Calcium to Rule Out Obstructive Coronary Artery Disease in Patients with Acute Chest Pain. *JACC Cardiovasc. Imaging* **2022**, *15*, 271–280. [CrossRef] [PubMed]
99. Fujimoto, D.; Kinoshita, D.; Suzuki, K.; Niida, T.; Yuki, H.; McNulty, I.; Lee, H.; Otake, H.; Shite, J.; Ferencik, M.; et al. Coronary spotty calcification, compared with macro calcification, is associated with a higher level of vascular inflammation and plaque vulnerability in patients with stable angina. *Atherosclerosis* **2025**, *405*, 119237. [CrossRef] [PubMed]
100. Sakaguchi, M.; Hasegawa, T.; Ehara, S.; Matsumoto, K.; Mizutani, K.; Iguchi, T.; Ishii, H.; Nakagawa, M.; Shimada, K.; Yoshiyama, M. New insights into spotty calcification and plaque rupture in acute coronary syndrome: An optical coherence tomography study. *Heart Vessel.* **2016**, *31*, 1915–1922. [CrossRef] [PubMed]
101. Kataoka, Y.; Puri, R.; Hammadah, M.; Duggal, B.; Uno, K.; Kapadia, S.R.; Tuzcu, E.M.; Nissen, S.E.; Nicholls, S.J. Spotty calcification and plaque vulnerability in vivo: Frequency-domain optical coherence tomography analysis. *Cardiovasc. Diagn. Ther.* **2014**, *4*, 460–469. [CrossRef] [PubMed] [PubMed Central]
102. Shi, X.; Gao, J.; Lv, Q.; Cai, H.; Wang, F.; Ye, R.; Liu, X. Calcification in Atherosclerotic Plaque Vulnerability: Friend or Foe? *Front. Physiol.* **2020**, *11*, 56. [CrossRef] [PubMed] [PubMed Central]
103. Kinoshita, D.; Suzuki, K.; Yuki, H.; Niida, T.; Fujimoto, D.; Minami, Y.; Dey, D.; Lee, H.; McNulty, I.; Ako, J.; et al. Coronary plaque phenotype associated with positive remodeling. *J. Cardiovasc. Comput. Tomogr.* **2024**, *18*, 401–407. [CrossRef] [PubMed]
104. Zhao, J.; Wu, T.; Tan, J.; Chen, Y.; Xu, X.; Guo, Y.; Jin, C.; Xiu, L.; Zhao, R.; Sun, S.; et al. Pancoronary plaque characteristics in STEMI patients with rapid plaque progression: An optical coherence tomography study. *Int. J. Cardiol.* **2024**, *400*, 131821. [CrossRef] [PubMed]
105. Russo, M.; Zimarino, M. Coronary calcifications are the growth rings of coronary atherosclerotic plaque. *Int. J. Cardiol.* **2025**, *442*, 133902. [CrossRef] [PubMed]
106. Lee, T.; Mintz, G.S.; Matsumura, M.; Zhang, W.; Cao, Y.; Usui, E.; Kanaji, Y.; Murai, T.; Yonetsu, T.; Kakuta, T.; et al. Prevalence, Predictors, and Clinical Presentation of a Calcified Nodule as Assessed by Optical Coherence Tomography. *JACC Cardiovasc. Imaging* **2017**, *10*, 883–891. [CrossRef] [PubMed]
107. Sugiyama, T.; Kakuta, T.; Hoshino, M.; Hada, M.; Yonetsu, T.; Usui, E.; Hanyu, Y.; Nagamine, T.; Nogami, K.; Ueno, H.; et al. Predictors of Optical Coherence Tomography-Defined Calcified Nodules in Patients with Acute Coronary Syndrome—A Substudy From the TACTICS Registry. *Circ. J.* **2024**, *88*, 1853–1861. [CrossRef] [PubMed]
108. Nelles, G.; Abdelwahed, Y.S.; Alyaqoob, A.; Seppelt, C.; Stähli, B.E.; Meteva, D.; Kränkel, N.; Haghikia, A.; Skurk, C.; Dreger, H.; et al. Spotty calcium deposits within acute coronary syndrome (ACS)-causing culprit lesions impact inflammatory vessel-wall interactions and are associated with higher cardiovascular event rates at one year follow-up: Results from the prospective translational OPTICO-ACS study program. *Atherosclerosis* **2023**, *385*, 117284. [CrossRef] [PubMed]
109. Prati, F.; Gatto, L.; Fabbiocchi, F.; Vergallo, R.; Paoletti, G.; Ruscica, G.; Marco, V.; Romagnoli, E.; Boi, A.; Fineschi, M.; et al. Clinical outcomes of calcified nodules detected by optical coherence tomography: A sub-analysis of the CLIMA study. *EuroIntervention* **2020**, *16*, 380–386. [CrossRef] [PubMed]
110. Yokomine, T.; Kajiya, T.; Takei, T.; Kitazono, K.; Ninomiya, T.; Inoue, T.; Takaoka, J.; Atsuchi, Y.; Atsuchi, N.; Ohishi, M. Impact of Calcified Nodules on Clinical Outcomes in Hemodialysis Patients Undergoing Percutaneous Coronary Intervention. *Am. J. Cardiol.* **2025**, *245*, 35–37. [CrossRef] [PubMed]
111. Lei, F.; Yin, Y.; Liu, X.; Fang, C.; Jiang, S.; Xu, X.; Sun, S.; Pei, X.; Jia, R.; Tang, C.; et al. Clinical Outcomes of Different Calcified Culprit Plaques in Patients with Acute Coronary Syndrome. *J. Clin. Med.* **2022**, *11*, 4018. [CrossRef] [PubMed] [PubMed Central]
112. Okamura, A.; Okura, H.; Iwai, S.; Sakagami, A.; Kamon, D.; Hashimoto, Y.; Ueda, T.; Soeda, T.; Watanabe, M.; Saito, Y. Incidence and prognostic impact of the calcified nodule in coronary artery disease patients with end-stage renal disease on dialysis. *Heart Vessel.* **2022**, *37*, 1662–1668. [CrossRef] [PubMed]
113. Sugizaki, Y.; Matsumura, M.; Chen, Y.; Tsukui, T.; Shlofmitz, E.; Thomas, S.V.; Malik, S.; Dakroub, A.; Singh, M.; Shin, D.; et al. Natural history of a newly developed calcified nodule: Incidence, predictors, and clinical outcomes. *EuroIntervention* **2024**, *20*, e1330–e1339. [CrossRef] [PubMed] [PubMed Central]
114. Rai, H.; Harzer, F.; Otsuka, T.; Abdelwahed, Y.S.; Antuña, P.; Blachutzik, F.; Koppara, T.; Räber, L.; Leistner, D.M.; Alfonso, F.; et al. Stent Optimization Using Optical Coherence Tomography and Its Prognostic Implications After Percutaneous Coronary Intervention. *J. Am. Heart Assoc.* **2022**, *11*, e023493. [CrossRef] [PubMed] [PubMed Central]
115. Nagata, T.; Minami, Y.; Katsura, A.; Asakura, K.; Katamine, M.; Muramatsu, Y.; Fujiyoshi, K.; Kinoshita, D.; Ako, J. Optical coherence tomography factors for adverse events in patients with severe coronary calcification. *Int. J. Cardiol.* **2023**, *376*, 28–34. [CrossRef] [PubMed]
116. Yamamoto, T.; Kawamori, H.; Toba, T.; Kakizaki, S.; Nakamura, K.; Fujimoto, D.; Sasaki, S.; Fujii, H.; Hamana, T.; Osumi, Y.; et al. Clinical impact of optical coherence tomography findings after drug-coated balloon treatment for patients with acute coronary syndromes. *Int. J. Cardiol.* **2023**, *387*, 131149. [CrossRef] [PubMed]

117. Fukui, K.; Koide, M.; Takamatsu, K.; Sugimoto, H.; Takeda, Y.; Akabame, S.; Seki, T.; Zen, K.; Matoba, S. Clinical Outcomes of Percutaneous Coronary Intervention Using Drug-Coated Balloons for De Novo Coronary Lesions with Eruptive Calcified Nodules as Detected by Optical Coherence Tomography. *Circ. J.* **2025**, *89*, 303–311. [CrossRef] [PubMed]
118. Shan, Y.; Lu, W.; Han, Z.; Pan, S.; Li, X.; Wang, X.; Pan, L.; Wang, X.; Zheng, X.; Li, R.; et al. Long-term outcomes of drug-coated balloon treatment of calcified coronary artery lesions: A multicenter, retrospective, propensity matching study. *Front. Cardiovasc. Med.* **2023**, *10*, 1122290. [CrossRef] [PubMed] [PubMed Central]
119. Jia, H.; Abtahian, F.; Aguirre, A.D.; Lee, S.; Chia, S.; Lowe, H.; Kato, K.; Yonetsu, T.; Vergallo, R.; Hu, S.; et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J. Am. Coll. Cardiol.* **2013**, *62*, 1748–1758. [CrossRef] [PubMed] [PubMed Central]
120. Davies, M.J.; Bland, J.M.; Hangartner, J.R.; Angelini, A.; Thomas, A.C. Factors influencing the presence or absence of acute coronary artery thrombi in sudden ischaemic death. *Eur. Heart J.* **1989**, *10*, 203–208. [CrossRef] [PubMed]
121. Vergallo, R.; Uemura, S.; Soeda, T.; Minami, Y.; Cho, J.M.; Ong, D.S.; Aguirre, A.D.; Gao, L.; Biasucci, L.M.; Crea, F.; et al. Prevalence and Predictors of Multiple Coronary Plaque Ruptures: In Vivo 3-Vessel Optical Coherence Tomography Imaging Study. *Arterioscler. Thromb. Vasc. Biol.* **2016**, *36*, 2229–2238. [CrossRef] [PubMed]
122. Volleberg, R.H.J.A.; Rroku, A.; Mol, J.Q.; Hermanides, R.S.; van Leeuwen, M.; Berta, B.; Meuwissen, M.; Alfonso, F.; Wojakowski, W.; Belkacemi, A.; et al. FFR-Negative Nonculprit High-Risk Plaques and Clinical Outcomes in High-Risk Populations: An Individual Patient-Data Pooled Analysis From COMBINE (OCT-FFR) and PECTUS-obs. *Circ. Cardiovasc. Interv.* **2025**, *18*, e014667. [CrossRef] [PubMed] [PubMed Central]
123. Kataoka, Y.; Hammadah, M.; Puri, R.; Duggal, B.; Uno, K.; Kapadia, S.R.; Murat Tuzcu, E.; Nissen, S.E.; Nicholls, S.J. Plaque microstructures in patients with coronary artery disease who achieved very low low-density lipoprotein cholesterol levels. *Atherosclerosis* **2015**, *242*, 490–495. [CrossRef] [PubMed]
124. Liu, S.; Hou, J.; Wan, J.; Yang, Y.; Wang, D.; Liang, D.; Wang, X.; Zhou, P.; Wang, P. Effect of Intensive Lipid-Lowering Therapy on Coronary Plaque Stabilization Derived from Optical Coherence Tomography: A Meta-analysis and Meta-regression. *Cardiovasc. Drugs Ther.* **2025**, *39*, 119–132. [CrossRef] [PubMed]
125. Cholesterol Treatment Trialists' (CTT) Collaborators; Mihaylova, B.; Emberson, J.; Blackwell, L.; Keech, A.; Simes, J.; Barnes, E.H.; Voysey, M.; Gray, A.; Collins, R.; et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. *Lancet* **2012**, *380*, 581–590. [CrossRef] [PubMed]
126. Okazaki, S.; Yokoyama, T.; Miyauchi, K.; Shimada, K.; Kurata, T.; Sato, H.; Daida, H. Early statin treatment in patients with acute coronary syndrome: Demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: The ESTABLISH Study. *Circulation* **2004**, *110*, 1061–1068. [CrossRef] [PubMed]
127. Zhang, X.; Feng, H.; Han, Y.; Yuan, X.; Jiang, M.; Wang, W.; Gao, L. Plaque Stabilization and Regression, from Mechanisms to Surveillance and Clinical Strategies. *Rev. Cardiovasc. Med.* **2024**, *25*, 459. [CrossRef] [PubMed] [PubMed Central]
128. Takagi, T.; Yoshida, K.; Akasaka, T.; Hozumi, T.; Morioka, S.; Yoshikawa, J. Intravascular ultrasound analysis of reduction in progression of coronary narrowing by treatment with pravastatin. *Am. J. Cardiol.* **1997**, *79*, 1673–1676. [CrossRef] [PubMed]
129. Dawson, L.P.; Lum, M.; Nerleker, N.; Nicholls, S.J.; Layland, J. Coronary Atherosclerotic Plaque Regression: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2022**, *79*, 66–82. [CrossRef] [PubMed]
130. Takayama, T.; Hiro, T.; Yamagishi, M.; Daida, H.; Hirayama, A.; Saito, S.; Yamaguchi, T.; Matsuzaki, M.; COSMOS Investigators. 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*, 2110–2117. [CrossRef] [PubMed]
131. Räber, L.; Taniwaki, M.; Zaugg, S.; Kelbæk, H.; Roffi, M.; Holmvang, L.; Noble, S.; Pedrazzini, G.; Moschovitis, A.; Lüscher, T.F.; 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.* **2015**, *36*, 490–500. [CrossRef] [PubMed]
132. Nissen, S.E.; Tuzcu, E.M.; Schoenhagen, P.; Brown, B.G.; Ganz, P.; Vogel, R.A.; Crowe, T.; Howard, G.; Cooper, C.J.; Brodie, B.; et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: A randomized controlled trial. *JAMA* **2004**, *291*, 1071–1080. [CrossRef] [PubMed]
133. Nicholls, S.J.; Ballantyne, C.M.; Barter, P.J.; Chapman, M.J.; Erbel, R.M.; Libby, P.; Raichlen, J.S.; Uno, K.; Borgman, M.; Wolski, K.; et al. Effect of two intensive statin regimens on progression of coronary disease. *N. Engl. J. Med.* **2011**, *365*, 2078–2087. [CrossRef] [PubMed]
134. Hiro, T.; Kimura, T.; Morimoto, T.; Miyauchi, K.; Nakagawa, Y.; Yamagishi, M.; Ozaki, Y.; Kimura, K.; Saito, S.; Yamaguchi, T.; et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: A multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). *J. Am. Coll. Cardiol.* **2009**, *54*, 293–302. [CrossRef] [PubMed]

135. Kini, A.S.; Baber, U.; Kovacic, J.C.; Limaye, A.; Ali, Z.A.; Sweeny, J.; Maehara, A.; Mehran, R.; Dangas, G.; Mintz, G.S.; 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*, 21–29. [CrossRef] [PubMed]
136. Komukai, K.; Kubo, T.; Kitabata, H.; Matsuo, Y.; Ozaki, Y.; Takarada, S.; Okumoto, Y.; Shiono, Y.; Orii, M.; Shimamura, K.; 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*, 2207–2217. [CrossRef] [PubMed]
137. Park, H.B.; Arsanjani, R.; Sung, J.M.; Heo, R.; Lee, B.K.; Lin, F.Y.; Hadamitzky, M.; Kim, Y.J.; Conte, E.; Andreini, D.; et al. Impact of statins based on high-risk plaque features on coronary plaque progression in mild stenosis lesions: Results from the PARADIGM study. *Eur. Heart J. Cardiovasc. Imaging* **2023**, *24*, 1536–1543. [CrossRef] [PubMed]
138. Kinoshita, D.; Suzuki, K.; Usui, E.; Hada, M.; Yuki, H.; Niida, T.; Minami, Y.; Lee, H.; McNulty, I.; Ako, J.; et al. High-Risk Plaques on Coronary Computed Tomography Angiography: Correlation with Optical Coherence Tomography. *JACC Cardiovasc. Imaging* **2024**, *17*, 382–391. [CrossRef] [PubMed]
139. Cannon, C.P.; Blazing, M.A.; Giugliano, R.P.; McCagg, A.; White, J.A.; Theroux, P.; Darius, H.; Lewis, B.S.; Ophuis, T.O.; Jukema, J.W.; et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N. Engl. J. Med.* **2015**, *372*, 2387–2397. [CrossRef] [PubMed]
140. Chai, B.; Shen, Y.; Li, Y.; Wang, X. Meta-analysis and trial sequential analysis of ezetimibe for coronary atherosclerotic plaque compositions. *Front. Pharmacol.* **2023**, *14*, 1166762. [CrossRef] [PubMed] [PubMed Central]
141. Zhang, Y.J.; Xu, M.; Duan, J.Q.; Wang, D.J.; Han, S.L. Effect of ezetimibe-statin combination therapy vs. statin monotherapy on coronary atheroma phenotype and lumen stenosis in patients with coronary artery disease: A meta-analysis and trial sequential analysis. *Front. Pharmacol.* **2024**, *15*, 1343582. [CrossRef] [PubMed] [PubMed Central]
142. Hibi, K.; Sonoda, S.; Kawasaki, M.; Otsuji, Y.; Murohara, T.; Ishii, H.; Sato, K.; Koshida, R.; Ozaki, Y.; Sata, M.; et al. Effects of Ezetimibe-Statin Combination Therapy on Coronary Atherosclerosis in Acute Coronary Syndrome. *Circ. J.* **2018**, *82*, 757–766. [CrossRef] [PubMed]
143. Habara, M.; Nasu, K.; Terashima, M.; Ko, E.; Yokota, D.; Ito, T.; Kurita, T.; Teramoto, T.; Kimura, M.; Kinoshita, Y.; et al. Impact on optical coherence tomographic coronary findings of fluvastatin alone versus fluvastatin + ezetimibe. *Am. J. Cardiol.* **2014**, *113*, 580–587. [CrossRef] [PubMed]
144. Hougaard, M.; Hansen, H.S.; Thayssen, P.; Maehara, A.; Antonsen, L.; Junker, A.; Mintz, G.S.; Jensen, L.O. Influence of Ezetimibe on Plaque Morphology in Patients with ST Elevation Myocardial Infarction Assessed by Optical Coherence Tomography: An OCTIVUS Sub-Study. *Cardiovasc. Revasc. Med.* **2020**, *21*, 1417–1424. [CrossRef] [PubMed]
145. Schwartz, G.G.; Steg, P.G.; Szarek, M.; Bhatt, D.L.; Bittner, V.A.; Diaz, R.; Edelberg, J.M.; Goodman, S.G.; Hanotin, C.; Harrington, R.A.; et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N. Engl. J. Med.* **2018**, *379*, 2097–2107. [CrossRef] [PubMed]
146. Sabatine, M.S.; Giugliano, R.P.; Keech, A.C.; Honarpour, N.; Wiviott, S.D.; Murphy, S.A.; Kuder, J.F.; Wang, H.; Liu, T.; Wasserman, S.M.; et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N. Engl. J. Med.* **2017**, *376*, 1713–1722. [CrossRef] [PubMed]
147. Nicholls, S.J.; Puri, R.; Anderson, T.; Ballantyne, C.M.; Cho, L.; Kastelein, J.J.; Koenig, W.; Somaratne, R.; Kassahun, H.; Yang, J.; et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA* **2016**, *316*, 2373–2384. [CrossRef] [PubMed]
148. Ako, J.; Hibi, K.; Tsujita, K.; Hiro, T.; Morino, Y.; Kozuma, K.; Shinke, T.; Otake, H.; Uno, K.; Louie, M.J.; 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*, 2025–2033. [CrossRef] [PubMed]
149. Nicholls, S.J.; Kataoka, Y.; Nissen, S.E.; Prati, F.; Windecker, S.; Puri, R.; Hucko, T.; Aradi, D.; Herrman, J.R.; Hermanides, R.S.; et al. Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction. *JACC Cardiovasc. Imaging* **2022**, *15*, 1308–1321. [CrossRef] [PubMed]
150. Räber, L.; Ueki, Y.; Otsuka, T.; Losdat, S.; Häner, J.D.; Lonborg, J.; Fahrni, G.; Iglesias, J.F.; van Geuns, R.J.; Ondracek, A.S.; 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*, 1771–1781. [CrossRef] [PubMed] [PubMed Central]
151. Ray, K.K.; Wright, R.S.; Kallend, D.; Koenig, W.; Leiter, L.A.; Raal, F.J.; Bisch, J.A.; Richardson, T.; Jaros, M.; Wijngaard, P.L.J.; et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N. Engl. J. Med.* **2020**, *382*, 1507–1519. [CrossRef] [PubMed]
152. Revaiah, P.C.; Serruys, P.W.; Onuma, Y.; Andreini, D.; Budoff, M.J.; Sharif, F.; Chernofsky, A.; Vikarunnessa, S.; Wiethoff, A.J.; Yates, D.; et al. Design and rationale of a randomized clinical trial assessing the effect of inclisiran on atherosclerotic plaque in individuals without previous cardiovascular event and without flow-limiting lesions identified in an in-hospital screening: The VICTORION-PLAQUE primary prevention trial. *Am. Heart J.* **2026**, *291*, 199–212. [CrossRef] [PubMed]

153. Ridker, P.M.; Everett, B.M.; Thuren, T.; MacFadyen, J.G.; Chang, W.H.; Ballantyne, C.; Fonseca, F.; Nicolau, J.; Koenig, W.; Anker, S.D.; et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N. Engl. J. Med.* **2017**, *377*, 1119–1131. [CrossRef] [PubMed]
154. Galiè, N.; Guarnieri, C.; Ussia, G.P.; Zimarino, M.; Traini, A.M.; Parlangeli, R.; Vaona, I.; Branzi, A.; Magnani, B. Limitation of myocardial infarct size by nicorandil after sustained ischemia in pigs. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 477–484. [CrossRef] [PubMed]
155. Giordano, S.; Camera, M.; Brambilla, M.; Sarto, G.; Spadafora, L.; Bernardi, M.; Iaconelli, A.; D'Amario, D.; Biondi-Zoccai, G.; Celia, A.I.; et al. Combining Colchicine and Antiplatelet Therapy to Tackle Atherothrombosis: A Paradigm in Transition? *Int. J. Mol. Sci.* **2025**, *26*, 1136. [CrossRef] [PubMed] [PubMed Central]
156. Nidorf, S.M.; Fiolet, A.T.L.; Mosterd, A.; Eikelboom, J.W.; Schut, A.; Opstal, T.S.J.; The, S.H.K.; Xu, X.F.; Ireland, M.A.; Lenderink, T.; et al. Colchicine in Patients with Chronic Coronary Disease. *N. Engl. J. Med.* **2020**, *383*, 1838–1847. [CrossRef] [PubMed]
157. Andreis, A.; Imazio, M.; Piroli, F.; Avondo, S.; Casula, M.; Paneva, E.; De Ferrari, G.M. Efficacy and safety of colchicine for the prevention of major cardiovascular and cerebrovascular events in patients with coronary artery disease: A systematic review and meta-analysis on 12,869 patients. *Eur. J. Prev. Cardiol.* **2022**, *28*, 1916–1925. [CrossRef] [PubMed]
158. Yu, M.; Yang, Y.; Dong, S.L.; Zhao, C.; Yang, F.; Yuan, Y.F.; Liao, Y.H.; He, S.L.; Liu, K.; Wei, F.; et al. Effect of Colchicine on Coronary Plaque Stability in Acute Coronary Syndrome as Assessed by Optical Coherence Tomography: The COLOCT Randomized Clinical Trial. *Circulation* **2024**, *150*, 981–993. [CrossRef] [PubMed]
159. Psaltis, P.J.; Nguyen, M.T.; Singh, K.; Sinhal, A.; Wong, D.T.L.; Alcock, R.; Rajendran, S.; Dautov, R.; Barlis, P.; Patel, S.; et al. Optical coherence tomography assessment of the impact of colchicine on non-culprit coronary plaque composition after myocardial infarction. *Cardiovasc. Res.* **2025**, *121*, 468–478. [CrossRef] [PubMed]
160. Wykrzykowska, J.J.; Diletti, R.; Gutierrez-Chico, J.L.; van Geuns, R.J.; van der Giessen, W.J.; Ramcharitar, S.; Duckers, H.E.; Schultz, C.; de Feyter, P.; van der Ent, M.; 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*, 945–954. [CrossRef] [PubMed]
161. Stone, G.W.; Maehara, A.; Ali, Z.A.; Held, C.; Matsumura, M.; Kjøller-Hansen, L.; Bøtker, H.E.; Maeng, M.; Engstrøm, T.; Wiseth, R.; et al. Percutaneous Coronary Intervention for Vulnerable Coronary Atherosclerotic Plaque. *J. Am. Coll. Cardiol.* **2020**, *76*, 2289–2301. [CrossRef] [PubMed]
162. Zimarino, M.; Renda, G.; De Caterina, R. Optimal duration of antiplatelet therapy in recipients of coronary drug-eluting stents. *Drugs* **2005**, *65*, 725–732. [CrossRef] [PubMed]
163. Zimarino, M.; Angiolillo, D.J.; Dangas, G.; Capodanno, D.; Barbato, E.; Hahn, J.Y.; Giustino, G.; Watanabe, H.; Costa, F.; Cuisset, T.; et al. Antithrombotic therapy after percutaneous coronary intervention of bifurcation lesions. *EuroIntervention* **2021**, *17*, 59–66. [CrossRef] [PubMed] [PubMed Central]