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Evaluation and Management of the Vulnerable Plaque

Anne Cornelissen[1,2] · Hiroyuki Jinnouchi[1] · Atsushi Sakamoto[1] · Sho Torii[1,3] · Salome Kuntz[1] · Liang Guo[1] · Raquel Fernandez[1] · Kay Paek[1] · Christina Mayhew[1] · Matthew Kutyna[1] · Maria E. Romero[1] · Frank D. Kolodgie[1] · Renu Virmani[1] · Aloke V. Finn[1,4]

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Abstract

Purpose of Review Coronary plaque rupture is the dominant mechanism of acute myocardial infarction and sudden coronary death. If we are to make a major inroads on reducing morbidity and mortality from cardiovascular disease, more accurate prediction of an individual's near-term cardiovascular risk (i.e., prediction of future coronary events) than what we can offer today is the ultimate goal to enable a more patient-tailored treatment strategy for coronary artery disease. In this review, we address the value of the vulnerable plaque concept in the context of an integrative cardiovascular risk assessment.

Recent Findings Even with today's state-of-the-art intravascular and non-invasive imaging, the identification of plaques at high-risk for rupture remains an elusive task albeit one in which important progress continues to be made. The vulnerable plaque concept emerged from the identification of morphological characteristics associated with plaque rupture as identified by autopsy studies. However, morphology alone may only be one of many factors which drive plaque progression. Therefore, the usefulness of the classical vulnerable plaque concept for predicting an individual's cardiovascular risk clearly remains in the research realm. Nonetheless, the potential of being able to predict events before they happen remains an issue of utmost importance for cardiology.

Summary The identification of patients at risk for adverse cardiovascular events requires a comprehensive risk assessment. Invasive and non-invasive coronary imaging techniques allow for a detailed detection of vulnerable plaque characteristics. In combination with systemic factors that increase the disease's activity, the finding that an individual may harbor coronary plaques with vulnerable characteristics indicates elevated atherosclerotic disease risk and thus justifies a more intensive therapeutic approach.

Keywords Coronary artery disease · Plaque rupture · Thin-cap fibroatheroma · Risk factor · Risk assessment strategy

Introduction

Coronary artery disease (CAD) continues to be a leading cause of death in the USA and elsewhere despite advances in the surgical and percutaneous treatment of coronary atherosclerosis [1]. It is the most common substrate underlying sudden cardiac death (SCD), an unexpected natural death from a coronary cause within a short period of time (usually ≤ 1 h from the onset of symptoms). There are more than 365,000 out of hospital cardiac arrests annually in the USA with nearly 90% of them being fatal. Most acute cardiac events occur in the context of plaque-related intracoronary thrombus formation [2].

Modern cardiology focuses on improving techniques to restore blood flow in coronary arteries with significant stenosis or occlusions causing cardiac ischemia and infarction. This reactive strategy does not prevent future coronary events, and thus the incidence of SCD due to obstructive CAD continues to remain largely unchanged. Moreover, our ability to predict who is at risk on a patient-specific basis in the absence of symptoms is poor. Although pharmacotherapy with agents such as aspirin and statins has been proven to lower the risk of future coronary events, recurrent events continue to occur even in treated patients. Moreover, a substantial number of patients die without initialization of proper therapy.

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✉ Aloke V. Finn
afinn@CVPath.org

[1] CVPath Institute, Inc., 19 Firstfield Road, Gaithersburg, MD 20878, USA

[2] Department of Cardiology, University Hospital RWTH Aachen, Aachen, Germany

[3] Department of Cardiology, Tokai University School of Medicine, Isehara, Kanagawa, Japan

[4] School of Medicine, University of Maryland, Baltimore, MD, USA

If we are to make a major inroad on reducing morbidity and mortality from CAD, major advances in cardiology will require a more sophisticated approach resulting in the ability to predict risk of further coronary events on an individual basis. Different aspects of plaque vulnerability have been demonstrated as independent predictors for major adverse cardiac events (MACE). Therefore, it is essential to further identify meaningful markers related to those plaques at near-term risk of instability. This might be achieved by imaging-based means. Another approach would be to identify the vulnerable patient, defined by high atherosclerotic burden, high-risk/vulnerable plaques, or thrombogenic blood. Such a patient-specific approach might be conducted by biomarkers which would indirectly be linked to the existence of vulnerable plaques. In this review, we will discuss the current state of knowledge with regard to evaluation and management of vulnerable plaques.

Vulnerable Plaque Pathology

Improvement in our understanding of the pathophysiology of myocardial infarction (MI) was an essential step in advancing the concept and definition of vulnerable plaque. Early studies by a number of investigators provided definitive evidence that intracoronary thrombi had a causal role in the pathogenesis of myocardial infarction [3].

Post-mortem studies have identified three distinct morphologic entities leading to intracoronary thrombosis: plaque rupture, plaque erosion, and calcified nodules [4]. From our analysis of greater than 800 cases of sudden coronary death with evidence of luminal thrombosis at autopsy, plaque rupture was responsible for the majority (68.2%) of coronary thrombosis [3]. A worldwide review of 22 autopsy studies including 1847 coronary arteries revealed 73% fatal coronary thrombi developed on top of a ruptured atherosclerotic plaque [5]. Rupture means a structural defect in the fibrous cap that separates the highly thrombogenic plaque contents from the blood stream [6]. The exposure of the lipid-rich necrotic core to the blood activates the coagulation cascade, resulting in the occlusion of the coronary artery by thrombus formation. As will be discussed below, the vulnerable plaque paradigm is largely based on the mechanisms thought to promote plaque rupture.

Plaque erosion represents the second most common cause of intracoronary thrombosis. In our own autopsy series, plaque erosion accounts for 28.5% of cases of sudden coronary deaths. Erosion can be defined as intracoronary thrombus formation without evidence of plaque rupture [4]. Histopathologic studies have revealed denudation of the endothelial layer at the erosion site, leading to exposure of the proteoglycan and smooth muscle cell–rich intima [4]. Usually the underlying plaque is fibroatheroma. Recently, in vivo classification of the causes of coronary artery thrombosis has been assisted by the development of optical coherence tomography (OCT) [7], a high-resolution intravascular imaging technique that measures backscattered light, or optical echoes, derived from an infrared light source. OCT studies of patients with acute coronary syndromes (ACS) revealed a 27–31% prevalence of plaque erosion [8, 9]. Both pathology and OCT studies agree that plaque erosion is more frequent in younger individuals, is more likely to occur in women (with a higher prevalence in younger women (i.e., < 50 years of age)), and is more likely in smokers [9–11]. Other coronary risk factors such as diabetes, hypertension, hyperlipidemia, and chronic kidney disease (CKD) are less common in erosion versus rupture [12, 13]. Although perturbations in shear have been implicated in the pathogenesis of plaque erosion [14], the precursor lesion to thrombotic plaque erosion is not known. Thus, the concept of vulnerable plaque pertaining to erosions has not been developed.

A third but rare mechanism underlying sudden thrombotic vessel occlusion is calcified nodule [4]. We reported an incidence of 3.3% from our own collection of sudden coronary death autopsies [4], and the incidence was 6% in clinical studies [15•]. According to the pathologic definition, the calcified nodule is characterized as a disrupted luminal surface by nodules of dense calcium with overlying thrombus and little or no underlying necrotic core in arteries that are highly calcified, tortuous, and often have large sheets of calcification. Because the precise mechanisms of calcified nodule formation remain unclear, its precursor lesion is unknown. It is believed that fragmentation of calcified plates/sheets is one of the underlying mechanisms [16•]. Breaks in calcified plates/sheets lead to small nodules of calcification which disrupt the overlying fibrous cap and endothelial lining which attracts platelets and fibrin leading to luminal thrombus. The location of calcified nodule is most frequent in the mid-right coronary artery or left anterior descending artery—sites of maximal torsion [4].

The Thin-Cap Fibroatheroma—Features of Vulnerability

The concept and definition of vulnerable plaque arose from the notion that myocardial infarction (MI) frequently developed in areas of non-severe coronary plaques which were subsequently referred to as "vulnerable plaques" by James Muller in the 1980s [17, 18].

The morphological criteria that define the vulnerable plaque arose from the concept that lesions that precede plaque rupture must resemble it. Ruptured plaques usually are characterized by a large necrotic core with a ruptured thin fibrous cap infiltrated by macrophages and T lymphocytes with few or no smooth muscle cells. The thickness of the fibrous cap near the rupture site measured 23 ± 19 μm, with 95% of caps measuring < 65 μm [19, 20]. It is precisely those lesions with intact fibrous

caps of < 65 μm that are designated vulnerable plaques or thin-cap fibroatheroma (TCFA) as they are defined by plaque morphology (Fig. 1). Therefore, the current definition of vulnerability is exclusively applicable to plaque rupture.

TCFAs differ from ruptured plaques in many important ways including smaller necrotic cores, fewer macrophages within the fibrous cap, and less calcification [21, 22]. It is important to note that the vulnerable plaque was not recognized in the American Heart Association consensus document [23] but was highlighted in a modified classification scheme published in 2000 [4]. One of the missing links in the AHA classification was the understanding that the fibrous cap undergoes thinning before rupture [19, 24].

In cases of sudden coronary death with evidence of plaque rupture, additional lesion sites typically show evidence of TCFAs in 70% of cases [25]. Such plaques are much less frequent (around 30%) in cases where death is associated with flow-limiting fibrocalcific plaques. These findings suggest that the temporal association between the presence of TCFA and rupture is not linear (i.e., some TCFAs may progress to rupture while others clearly do not) [22]. Most TCFAs occur in the proximal portion of the major coronary arteries [26, 27]. While basic studies have revealed that inflammation [28–30], increased enzymatic activity [31, 32], and core expansion [33, 34] all increase as TCFAs transform into unstable plaques, precise critical pathologic features which lead to plaque transformation remain unknown.

The Vulnerable Plaque—a Clinically Relevant Model?

Although pathologic studies and clinical terms have promoted the idea of precursor lesion to plaque rupture that could be located and treated before they cause coronary events, actual cause and effect data are missing in vivo. Advances in technology allow for a more detailed imaging, new biomarkers, and improved local and even systemic treatments of atherosclerosis. Catheter-based imaging techniques, notably intravascular ultrasound (IVUS-)-virtual histology and OCT as well as others, are able to identify "vulnerable" characteristics in atherosclerotic lesions in our daily practice. In this context, enormous efforts have been undertaken to recognize vulnerable plaques with the ultimate goals that once identified we would be able to treat them before an event can occur [35, 36]. In vivo studies in humans have not generally supported the theory that TCFAs as defined by intravascular imaging go on to cause clinical events. PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) was a prospective study of 697 patients with ACS who underwent three-vessel coronary angiography and gray-scale and radiofrequency intravascular ultrasonographic (IVUS) imaging [37]. From 595 identified thin-cap fibroatheromas, only 26 sites had a coronary event at a median follow-up of 3.4 years [37]. When combined with other criteria such as a plaque burden of 70% or more and a minimum lumen area of 4 mm^2 or less, the hazard ratio increased to 11.05 for any lesion having these criteria, yet 88.2% of patients harboring these plaques did not go on to have an event during the study [37]. Similar results were obtained in another IVUS study but with a lower number of patients and shorter duration of follow-up [38].

High-resolution imaging modalities such as OCT are able to measure plaque cap thickness [39] that has emerged as the best discriminator of plaque type in autopsy studies [19, 20, 40]. Confirming findings from post-mortem studies, the likelihood of a plaque to rupture depended on the fibrous cap thickness in a study investigating 126 plaques by means of OCT and IVUS [41]. In 82 patients, cap thickness was thinner in ruptured plaques than in TCFA (43 ± 11 μm vs. 56 ± 9 μm, $p < 0.001$) [41]. Another OCT study including 643 atherosclerotic plaques from 255 patients demonstrated that TCFAs were highly prevalent in various stages of coronary atherosclerotic disease, confirming their dynamic nature [42]. However, severely stenotic TCFAs had more features of plaque vulnerability and a greater plaque burden when compared with mildly stenotic TCFAs, suggesting that severely stenotic TCFAs might lead to clinical events in the near future as the thrombus formation following rupture would be more likely to further limit the blood flow [42]. Indeed, the combination of plaque burden and luminal narrowing was shown to be associated with ACS [41]. However, the ability of OCT to discriminate between calcified areas and lipid core is poor as both appear as signal poor regions [43].

Other intravascular imaging modalities such as near-infrared spectroscopy (NIRS) are clinically available, and recently the Lipid Rich Plaque Study was presented at the Transcatheter Cardiovascular Therapeutics Conference in September 2018 in San Diego, CA [44, 45]. A total of 1563 patients with suspected CAD underwent cardiac catheterization with percutaneous coronary intervention (PCI) for an index event. NIRS-IVUS imaging was performed in two or more non-culprit arteries, and patient- and plaque-level events were recorded for 2 years among those with at least one maximum lipid burden core index (max LCBI) 4-mm segment ≥ 250 and a randomly selected 50% of patients with max LCBI 4-mm segments < 250. The adjusted patient-level analysis found an 18% higher risk of experiencing a non-culprit event within 24 months for each 100-unit increase in LCBI 4-mm segment. While these data suggest plaque interrogation can predict overall risk of events, data on an individual plaque basis was not presented. Thus, on a patient- and plaque-specific basis, the technology could not discriminate the future risk of events in the near term for a specific plaque.

Complicating the paradigm of the vulnerable plaque is the fact that even plaque rupture does not always result in acute

MI or SCD [46] and can occur clinically silent [47]. Arbab-Zadeh et al. recently reviewed 11 clinical and pathological studies including 1371 patients and identified subclinical plaque rupture in 11.5% of patients with stable coronary artery disease and non-culprit plaque rupture in 21.5% of patients who presented with ACS [47]. Davies advanced the concept that repeated silent plaque ruptures are the cause of lumen compromise which may heal and cause progressive luminal narrowing as thrombus is incorporated into the lesion [48]. A histopathologic study including 142 cases identified prior healed rupture sites in 33 of 44 (75%) cases of acute plaque ruptures [49] (Fig. 1). In the same study, we showed that in patients dying of stable plaque, healed plaque rupture sites were identified in 80% of cases. Also, as the number of healed plaque ruptures in one location increased, so did the percent stenosis. An IVUS study demonstrated that 75% of TCFAs convert into thick-capped fibroatheromas within a 12-month period, presumably due to rupture and healing [50]. Although rupture might not necessarily cause clinical events, it still leads to plaque progression. Arteries with acute plaque rupture showed evidence of previous ruptures, and acute ruptures overlying healed ruptures were more narrowed than de novo ruptures, suggesting that repetitive injury may cause plaque enlargement [49]. Histopathologic studies almost invariably confirmed the presence of healed subclinical plaque rupture in lesions with advanced lumen narrowing (> 50% stenosis) [48, 49] (Fig. 1). These data reveal the troubling reality that even if we were able to correctly locate the vulnerable plaque, many of these would not cause clinically important symptomatic events.

On the other hand, patients harboring plaques with vulnerable characteristics, especially the finding of thin fibrous caps, can be considered at elevated risk for coronary events. Multiple ruptured plaques and non-ruptured TCFAs have been detected in addition to culprit lesions in patients with ACS, suggesting a systemic character of vulnerability throughout the coronary system [5, 20] and drawing attention toward a more systemic view on the "vulnerable patient" [51, 52] (Fig. 2).

Rapid Plaque Progression as Critical Step

Most culprit lesions have been shown significant narrowing at the time of an acute coronary event. Overall TCFA lesions are not nearly as stenotic as plaque ruptures [40]. The average luminal stenosis of culprit lesions in patients with ST elevation myocardial infarction was reported as 66% ± 12% after thrombus aspiration [53]. In a post-mortem analysis, the mean luminal narrowing was only 59.6% for TCFAs at autopsy, but 73.3% for acute plaque ruptures [20] (Fig. 1). Another autopsy study showed that more than 75% cross-section area stenosis was seen in 70% of ruptures and 40% of TCFA; only 5% ruptures and 10% TCFA were < 50% narrowed, suggesting lesion progression as critical in the transformation of TCFA into ruptures [40]. This was confirmed by a retrospective study from the Dynamic Registry of the National Heart, Lung, and Blood Institute that investigated 3747 patients who underwent PCI [54]. Of these, 216 patients required a PCI for a recurrent event of a non-culprit lesion within 1 year. The mean diameter stenosis increased from 41.8% ± 20.8% at baseline to 83.9% ± 13.9% at the time of the subsequent PCI. Similarly, a study of four serial coronary angiographies within a 1-year period demonstrated a more rapid progression of the average diameter stenosis in lesions that finally led to an acute myocardial infarction [55]. Thus, it is conceivable that lesions undergo narrowing only months to weeks before a coronary event.

Glagov reported that arteries with plaques undergo a progressive remodeling (i.e., arterial wall expansion) that allows preservation of lumen size up to a point [56]. Luminal compromise only occurs once a plaque advances beyond 40% narrowing. The exact mechanisms of narrowing of a plaque remain to a certain extent unknown. Repeated subclinical cycles of rupture and healing can lead to progressive plaque expansion until vessel occlusion and the onset of symptoms [49].

Another important mechanism is plaque hemorrhage deriving from sites of neovascularization at the borders of the necrotic core. Newly formed blood vessels extend from the adventitia into the intima. As neovessels are incompetent, macromolecules and also erythrocytes leak into the plaque microenvironment [57]. The red blood cells are rich in free cholesterol and contribute to the expansion of the necrotic core region. Moreover, the fragility of the nascent vessels promotes intraplaque hemorrhage with further accelerated plaque growth. The extent of neovascularization was shown to correlate with luminal stenosis and the histological inflammatory reaction [58]. Ahmadi et al. proposed that rapid plaque progression of moderately severe vulnerable plaques was the critical step before MI in most cases [59••]. Thus, a shift from the static assessment of morphologic criteria toward a more dynamic concept with the detection of rapid plaque progression prior to a clinical event may identify vulnerable plaques with an increased potential for adverse outcomes [59••].

How Do We Assess Vulnerability in Cardiovascular Risk?

The American College of Cardiology and the American Heart Association recommend cardiovascular disease risk assessment for adults aged 20–79 years and reassessment every 4 to 6 years [60]. Efforts have been made to establish a comprehensive risk stratification for the determination of an individual's risk for cardiovascular events. Well-

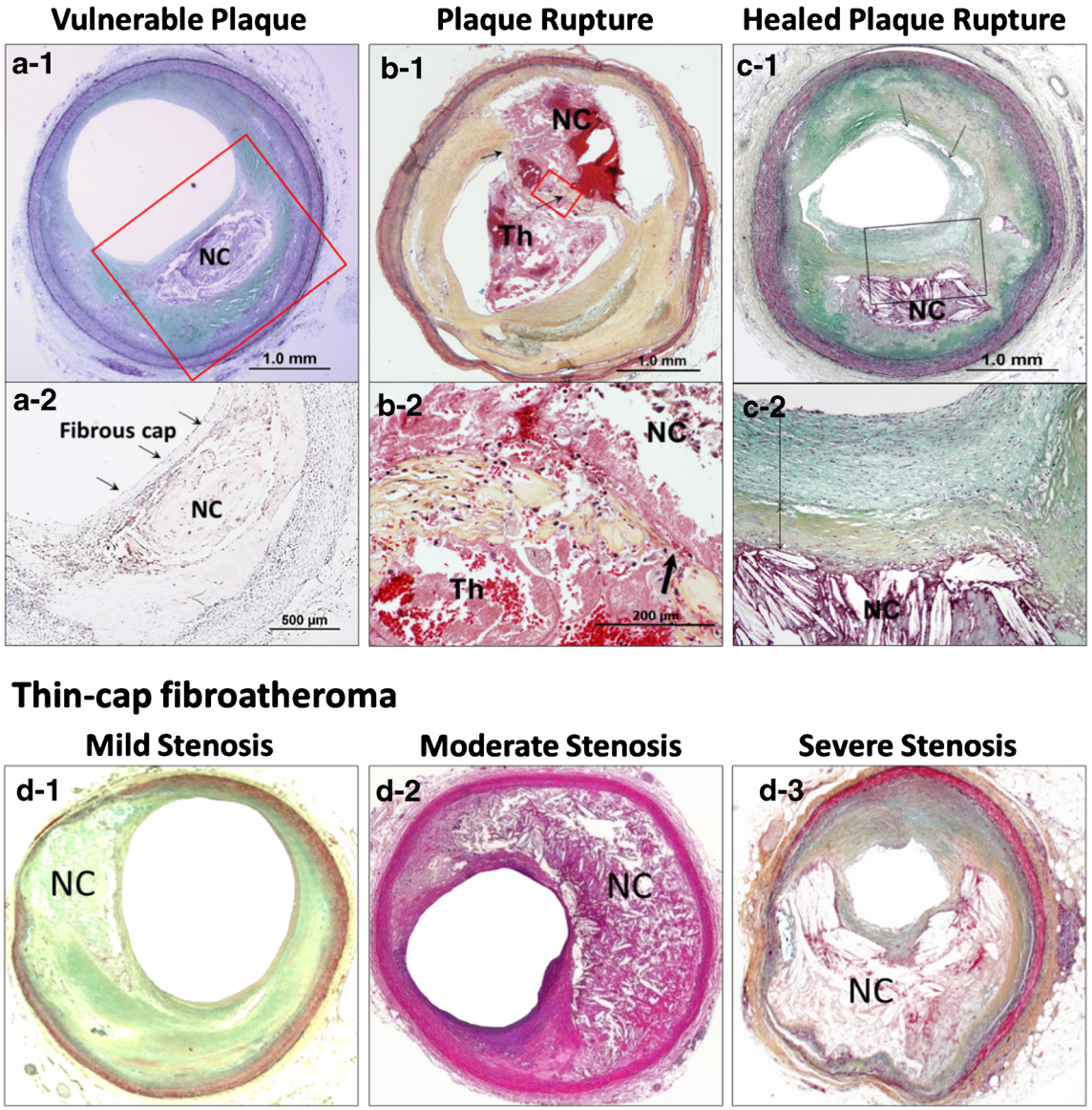

Fig. 1 **a-1**: vulnerable plaque with 60% narrowing. Note the presence of a NC and a thin, overlying fibrous cap. **a-2**: high-power view of the boxed area in a-1. Staining with anti-CD 68 antibody shows the presence of macrophages (brown) around the rim of the NC and in the fibrous cap. **b-1**: low-power view of a coronary artery showing plaque rupture (arrows) with an underlying necrotic core and a luminal thrombus. **b-2**: the high-power view of the boxed area in b-1 shows fibrous cap disruption (arrow) and the luminal thrombus communicating with the underlying NC. **c-1**: histological section of a coronary artery demonstrating a healed plaque rupture. **c-2**: high-power view of the boxed area in c-1 shows numerous smooth muscle cells within the newly formed proteoglycan-rich neointima (black double arrows close to the luminal surface), with clear demarcation from the underlying old collagen-rich fibrous cap. **d-1**–**d-3**: TCFA with mild (**d-1**), moderate (**d-2**), and severe luminal stenosis (**d-3**). The NC is covered by a thin fibrous cap. No thrombus is observed in the lumen, and the fibrous cap is intact. NC necrotic core, Th thrombus, TCFA thin-cap fibroatheroma. Panel **a** was reproduced with permission from Alfieri et al. Exploring unknowns in cardiology. *Nat Rev Cardiol*. 2014. 11(11):664–70. Panel **b** was reproduced with permission from Farb et al. [10]. Panel **c** was reproduced with permission from Otsuka et al. [7]. Panel **d** was reproduced with permission from Narula et al. [40]

validated prediction models and tools like the Framingham risk score [61], the SCORE (Systematic Coronary Risk Evaluation) [62], the Pooled Cohort Equations (PCE) [63], or the 2013 atherosclerotic cardiovascular disease (ASCVD) risk estimator [60] have been used successfully for cardiovascular risk assessment including the traditional risk factors age, sex, cholesterol level, cigarette smoking, and blood pressure. However, their usefulness as specific predictors for disease-related events is quite limited [64]. Most cardiovascular events occur in patients who were classified as "low or intermediate risk" by traditional risk factors [65]. Moreover, it seems to be a question of an individual's susceptibility to these risk factors that determine their harm.

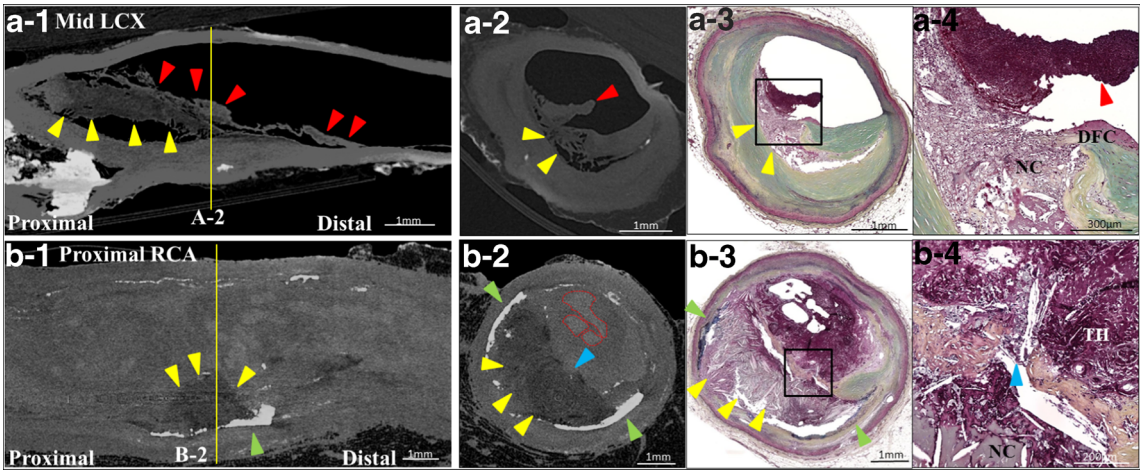

Fig. 2 Plaque rupture sites with correlation of histology and microcomputed tomography. Yellow lines in longitudinal images of micro-CT (**a-1** and **b-1**) correspond to the cross-section images in **a-2** and **b-2**. **a-1** and **a-2**: longitudinal and cross-section micro-CT images of the mid LCX showing irregularly dispersed luminal thrombus (red arrow heads) with an underlying lipid core plaque (yellow arrow heads). **a-3**: histological image matching the micro-CT image a-2. **a-4** is a high-power image corresponding to the black box in a-3, showing rupture site with an overlying thrombus (red arrow head). **b-1**: longitudinal micro-CT image of the proximal RCA showing a low-intensity area, which corresponds to the LCP in b-2 (yellow arrow heads) and fragmented calcification (green arrow heads) toward the media at the site of total occlusion. **b-2**: the cross-section micro-CT image shows a low-intensity area (yellow arrow heads), indicating NC and area of calcification (green arrow heads). Red dot line indicates formalin-filled space during micro-CT. **b-3**: the matching histological image shows the site of plaque rupture (the rupture site is highlighted in the black box) and underlying large NC (yellow arrow heads) which is surrounded abluminally by calcification (green arrow heads). **b-4** is a high-power image showing plaque rupture site (blue arrow). NC necrotic core, Th thrombus, CT computed tomography, LCX left circumflex artery, LCP lipid core plaque, RCA right coronary artery, DFC disrupted fibrous cap. Reproduced with permission from Jinnouchi et al. Micro-computed tomography demonstration of multiple plaque ruptures in a single individual presenting with sudden cardiac death. *Circ Cardiovasc Imaging*. 2018;11(10):e008331

Plaque burden has repeatedly been shown to be associated with the likelihood of cardiovascular events. Representing a non-invasive measuring tool of disease burden, coronary artery calcium (CAC) score has been proposed as an additional biomarker for advanced atherosclerotic cardiovascular disease risk assessment [66••]. Calcification seems to favor the transition from TCFA to rupture. When directly compared with ruptured plaques, thin-cap fibroatheromas exhibited less calcification within the fibrous cap [21]. Abdominal aortic calcification (AAC) correlates with CAC [67•, 68] and has been shown to predict cardiovascular events similarly [69]. Recently, non-enhanced CT-based AAC measurement could strongly predict future cardiovascular events in 829 generally healthy asymptomatic adults in a 10-year follow-up [70•].

A non-invasive assessment of plaque vulnerability by coronary computed tomography angiography (CCTA) was thought to improve the diagnostic accuracy for ACS during the index hospitalization. Indeed, vulnerable plaque features as assessed by CCTA were independent predictors for the presence of ACS in patients presenting with acute chest pain in the Rule Out Myocardial Ischemia/Infarction by Computer Assisted Tomography (ROMICAT-II) trial [71]. However, a retrospective analysis of the data recently revealed a longer length of stay, more downstream testing, more radiation exposure, and greater cost without an improvement in clinical outcomes if patients presented with acute chest pain, but had negative biomarkers and a non-ischemic ECG result [72•].

In clinical practice, it seems reasonable to embark on cardiovascular risk assessment based upon traditional risk factors as well as on common sense laboratory diagnostics. The additional assessment of non-traditional risk factors such as CAC might provide incremental value on discrimination and risk reclassification. However, we still lack direct evidence from adequately powered trials if this will improve patient health outcomes [73••]. The AHA/ACC risk assessment calculator presented in the 2013 guidelines which uses population-based formulas is still recommended to assess patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk [60]. However, among patients ≥ 40 years with an unclear risk status, calculating the CAC score is recommended to help with prevention and/or treatment decision-making [66]. Patients with a 0 CAC score are defined as having a generally low CVD risk for the next 10 years and can delay undergoing cholesterol-lowering medication therapy if they do not smoke and have no other high-risk characteristics.

Thus, patients in the gray-zone of "intermediate" risk would probably benefit from a more accurate imaging, as the finding of vulnerable plaque characteristics might justify a reclassification into a higher-risk group along with an intensified treatment strategy.

For patients with ASCVD 10-year risk ≥ 7.5%, lipid-lowering therapies with statins should be initiated [74]. Of course, decisions about starting anti-atherosclerotic therapies should be made on an individual basis with a patient's

physician and should take into account factors that have enhanced risk for CVD including smoking, weight, high blood sugar, inflammation, hypertension, and other factors (healthy diet, as well as physical activity) known to decrease CVD risk.

Treatment of Vulnerable Plaques

Lipid-Lowering Therapy

Reducing LDL cholesterol with statins has been associated with improvements in MACE in numerous clinical trials [75]. Statins have not only become a standard of care in the primary and secondary prevention of cardiovascular disease, but current guidelines also recommend early statin therapy in both ACS and prior to PCI [76, 77], as statins have demonstrated the ability to target several cellular pathways in acute inflammation and subsequent thrombosis [78]. A pooled analysis of 8 clinical trials including 4477 patients with high-risk plaques assessed with IVUS demonstrated a regression of atheroma burden under a statin therapy [79]. PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) exhibited statins being associated with slower progression of overall coronary atherosclerosis, a reduction of high-risk plaque features and increased plaque calcification [80••]. A high-intensity lipid-lowering therapy has proven to have the most beneficial effects in reduction of the incidence of heart attack, of revascularization, and of ischemic stroke. With each 1.0 mmol/L reduction, there is a drop in the annual rate of major vascular events by just over a fifth [81]. When comparing a low-intensity statin treatment to a high-intensity statin therapy, the latter was associated with less vulnerable plaque features [82].

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have recently emerged to significantly reduce LDL cholesterol levels when added to statin therapy [83]. Both alirocumab in ODYSSEY [84•] and evolocumab in FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) [85•] studies significantly reduced cardiovascular events at follow-up of 78 (ODYSSEY) and 48 (FOURIER) weeks. Thus, in 2017, the American College of Cardiology Task Force on Expert Consensus Decision published a focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL cholesterol lowering in the management of atherosclerotic cardiovascular disease risk [86•]. PCSK9 inhibitors can be considered for secondary prevention if patients with cardiovascular disease have a less-than-anticipated response (< 50% reduction in LDL-C and may consider ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL) to a maximally tolerated statin therapy and intensified lifestyle modification. In contrast, the addition of evolocumab to a statin did not produce differential changes in plaque composition compared with statin monotherapy as reported in the "Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV)" trial, which investigated 968 statin-treated CAD patients who underwent serial coronary IVUS imaging at baseline and following 76 weeks of treatment with placebo or evolocumab [87]. However, evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; difference, 17.0% [95% CI, 10.4 to 23.6%]; $P < 0.001$ for percent atheroma volume and 61.5% vs 48.9%; difference, 12.5% [95% CI, 5.9 to 19.2%]; $P < 0.001$ for total atheroma volume) [88••]. Regarding the limitations of IVUS imaging, it remains to be determined if alternative approaches to assessing plaque morphology might demonstrate plaque benefits of PCSK9 inhibition [88••].

Anti-Inflammatory Treatment

The inflammatory character of atherosclerosis has been known for more than two decades [89, 90]. In 1997, Ridker et al. demonstrated apparently healthy individuals with elevated levels of high-sensitive CRP (hsCRP) to be at high vascular risk irrespective of lipid levels [89]. Recently, the inflammatory character of atherosclerosis has come into the fore front with mixed results. Ridker et al. conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, in 10,061 patients with previous myocardial infarction with elevated hsCRP, a downstream biomarker of inflammation, during a follow-up period of 3.7 years [91•]. Only the 150-mg dose, but not the 50- and 300-mg doses, met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; $P = 0.005$). Canakinumab was associated with a higher incidence of fatal infection than was placebo [91•]. Thus, the data did not completely support the use of anti-inflammatory medicines as a method to decrease plaque vulnerability and the US Food and Drug Administration (FDA) did not support labeling for canakinumab as a targeted therapy for reduction of cardiovascular events. Similarly, a recent trial of low-dose methotrexate for the prevention of atherosclerotic events failed to reduce cardiovascular events versus placebo in the recently published trial [92•]. Considering the inflammatory characteristics of rupture-prone vulnerable plaques, anti-inflammatory treatment might decrease the risk of rupture but their efficacy has yet to be shown.

Invasive Treatment

Patients undergoing coronary angiography often present with multivessel disease, and the finding of vulnerable plaques is common. Current guidelines recommend primary PCI in lesions with significant coronary stenosis as defined as ≥ 70% luminal diameter narrowing or an epicardial stenosis or ≥ 50% luminal diameter narrowing of a left main stenosis [93]. Although vulnerable plaque characteristics are not established in the guidelines as determinants if or if not a plaque should undergo PCI, different aspects of plaque vulnerability have been demonstrated as independent predictors for MACE. To date, however, there is no evidence that pre-emptive treatment of vulnerable plaques is beneficial and the significance of imaging techniques in the assessment of vulnerable plaques still needs to be weighed out.

Conclusion

The identification of patients at risk for adverse cardiovascular events requires a comprehensive risk assessment. Major advancements of invasive and non-invasive coronary imaging techniques allow for a very detailed detection of vulnerable plaque characteristics, but the imaging information need to be put into a context. In combination with systemic factors that increase the disease's activity and the risk for vascular thrombosis, imaging might provide a more accurate picture of an individual's risk prediction. This approach has now been incorporated into the American College of Cardiology and the American Heart Association cardiovascular disease risk assessment through the use of computed tomography to evaluate coronary calcium. Regardless of the approach, the finding that an individual may harbor coronary plaques with vulnerable characteristics indicates elevated atherosclerotic disease risk and thus justifies a more intensive therapeutic approach.

Compliance with Ethical Standards

Conflict of Interest CVPath Institute has received institutional research support from 480 Biomedical, Abbott Vascular, ART, BioSensors International, Biotronik, Boston Scientific, Celonova, Claret Medical, Cook Medical, Cordis, Edwards Lifesciences, Medtronic, MicroPort, MicroVention, OrbusNeich, ReCore, SINO Medical Technology, Spectranetics, Surmodics, Terumo Corporation, W.L. Gore and Xeltis. R.V. has received honoraria from 480 Biomedical, Abbott Vascular, Boston Scientific, Cook Medical, Lutonix, Medtronic, Terumo Corporation and W.L. Gore; and is a consultant for 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore. A.V. Finn has received honoraria from Boston Scientific, Abbott Vascular, Amgen, and CeloNova. A.C. receives research grants from University Hospital RWTH Aachen.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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