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Detection of the Vulnerable Coronary Atherosclerotic Plaque—Promises and Limitations

Abhishek Sharma[1] · **Armin Arbab-Zadeh**[2]

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Abstract
Purpose of Review The merit of imaging "vulnerable atherosclerotic plaques" remains highly controversial. This review aims at providing current evidence for both its benefit and limitations.
Recent Findings Results from optical coherence tomography and intravascular ultrasound imaging in patients with coronary heart disease suggest that certain individual coronary atherosclerotic plaque characteristics, e.g., large lipid core in a fibroatheroma, are associated with greater risk of adverse patient outcome. However, a closer look at these studies reveals that these associations are confounded by the relationship of "vulnerable plaque" characteristics with baseline lumen obstruction, which is a known predictor of recurrent angina and the main component of the reported adverse patient outcome. Recent insights into the pathophysiology of acute coronary syndromes suggest it to be an exceedingly complex process involving numerous local and systemic factors, which hinders outcome prediction.
Summary The quest for the vulnerable plaque rests on the erroneous assumption that detecting coronary atherosclerotic lesions, which are prone to rupture or erode, will identify individuals at high risk of suffering acute coronary events. However, there is strong and consistent evidence suggesting that plaques most commonly rupture without associated clinical symptoms. Instead, ruptured plaques typically heal clinically silently and lead to plaque progression. The atherosclerotic disease burden, its metabolic activity, and risk factors for an inadequate response by the coagulation system to plaque disruption, on the other hand, are important predictors of acute coronary event risk and deserve our attention more than individual plaques.

Keywords Coronary artery disease · Coronary heart disease · Atherosclerosis · Acute coronary syndrome · Myocardial infarction · Sudden cardiac death

Abbreviations

ACS	Acute coronary syndrome
CAD	Coronary artery disease
CTA	Computed tomography angiography
IVUS	Intravascular ultrasound
TCFA	Thin-cap fibroatheroma

Introduction

Cardiovascular atherosclerotic disease continues to be the leading cause of mortality in the Western world [1]. In the USA alone, more than one million patients suffer an acute coronary event each year [1]. Accordingly, early identification of patients who are at high risk of suffering acute coronary events remains an important focus for researchers, policy makers, and healthcare providers [2].

Until recently, identification and treatment of patients with *obstructive* coronary artery disease (CAD) have been the

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✉ Armin Arbab-Zadeh
azadeh1@jhmi.edu

[1] Division of Cardiovascular Medicine, State University of New York Downstate Medical Center, New York, NY, USA

[2] Department of Medicine/Cardiology Division, Johns Hopkins University, Baltimore, MD, USA

primary focus in clinical practice. This approach was based on evidence that myocardial ischemia is provoked once a critical coronary arterial lumen narrowing is reached, typically 50–70% diameter stenosis [3, 4]. However, pathology studies revealed that culprit lesions in acute coronary syndrome (ACS) often have <50% lumen stenosis [5, 6]. Imaging studies confirmed that patients with non-obstructive CAD, i.e., with less than 50% stenoses, are at considerably greater risk of ACS and cardiac death compared to individuals without coronary atherosclerotic disease [7•, 8, 9].

In the past decades, our understanding of pathophysiology of ACS has significantly evolved. Since ACS can be the first manifestation of CAD in a significant proportion of "at-risk" otherwise asymptomatic individuals, research efforts aiming to identify "high-risk" characteristics is a major healthcare priority. Traditional risk assessment tools such as Framingham risk score, comprising various traditional risk factors for CAD (hypertension, diabetes, and hyperlipidemia), have been used to risk stratify asymptomatic individuals [10]. However, these scores are based on population studies and they have shown to be of modest accuracy for risk assessment in individuals [11]. Since certain atherosclerotic plaque characteristics, such as ruptured or eroded plaques, are commonly implicated in triggering ACS, there is considerable interest in identifying these features as potential indicators for high risk of ensuing events in patients [12, 13]. The concept of "vulnerable plaque" was introduced about almost three decades ago based on pathology studies of patients experiencing sudden cardiac death or ACS event. In this review, we summarize the data on detecting "vulnerable plaques" and the evidence of the associated clinical impact.

The Vulnerable Plaque: History and Concept

Although, the concept of plaque rupture as potential cause of sudden cardiac death was reported as early as 1844, it was not until more than a century later when James E. Muller categorized the "dangerous hemodynamically insignificant" lesion as vulnerable plaque [14–16]. Pathology studies reported three common characteristics of atherosclerotic lesions responsible for luminal thrombosis in acute myocardial infarction: plaque rupture, erosion, and calcified nodules, with former two accounting for more than 90% of cases [12, 13]. Plaque rupture typically occurs in a thin-cap fibroatheroma (TCFA) due to inflammation and sheer stress, leading to exposure of its thrombogenic necrotic core to the blood stream. In plaque erosion, the necrotic core remains intact but the overlaying endothelium is disrupted which may trigger local or vascular thrombosis.

Postmortem studies evaluating coronary and carotid plaques have identified several features of vulnerable plaques, which may increase the risk of triggering thrombosis, such as presence of a very thin fibrous cap, a large necrotic core, neovascularization, intraplaque hemorrhage, and microcalcifications [17, 18]. Because TCFA has been the plaque type most commonly associated with plaque rupture in several pathological and clinical studies, it has gained considerable attention as a target for imaging [17, 18, 19•, 20]. In a TCFA, a very thin fibrous tissue cap (mean thickness 23 μm) separates the necrotic core from the vascular lumen. In an autopsy study of 295 atherosclerotic coronary plaques, Narula and colleagues reported a cap thickness <55 μm as the best predictor of plaque rupture, followed by macrophage infiltration and necrotic core size [17]. TCFA plaque progression occurs primarily by fatty infiltration in early stages, followed by a gradual increase in necrotic core volume due to macrophage infiltration and intraplaque hemorrhage [18, 20–22].

Clinical Evidence of Vulnerable Plaque Imaging for Predicting Myocardial Infarction and Death

Several clinical studies investigated in vivo imaging tools for identifying rupture-prone vulnerable plaques to determine the risk of future adverse cardiovascular events. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree study (PROSPECT) prospectively investigated the rates of adverse cardiovascular events in almost 700 patients after an acute coronary event with target vessel revascularization, according to types of coronary plaques characterized by intravascular ultrasound (IVUS) imaging [19•]. After a median 3.4-year follow-up, almost half of subsequent cardiovascular events were attributable to non-culprit index lesions [19•]. In non-culprit index lesions, which resulted in subsequent ACS, there was progression of atherosclerosis from mean stenosis of 32 ± 21% to 65 ± 16% [19•]. Independent predictors of adverse cardiovascular events included individual atherosclerotic plaque burden >70%, minimum lumen area <4 mm^2, and TCFA [19•]. However, only six of 74 cardiovascular events were acute infarcts or death with the remaining events being hospitalization for chest pain during follow-up. Given that lesions with greater baseline lumen narrowing are more likely to progress to significant stenosis than plaques with milder baseline stenosis, it is not surprising that these features were predictive of cardiovascular events (=development of angina). Though PROSPECT investigators identified 596 TCFAs at non-culprit sites, only six myocardial infarctions were associated with them after more than 3 years follow-up. Thus, the PROSPECT study provided compelling evidence that the risk of myocardial infarction and death 3 years after detecting TCFA—the vulnerable plaque—is indeed small and far less than previously assumed [19•, 23, 24]. Very similar results were reported in the VIVA study, including 170 patients who had plaque characterization by virtual histology intravascular ultrasound during index PCI for with stable angina or ACS [25].

Optical coherence tomography (OCT) has been used for more detailed in vivo plaque characteristics than IVUS [26]. Tian and colleagues used combination of OCT and IVUS imaging to study characteristics of ruptured culprit and non-culprit plaques and non-ruptured TCFA in patients with ACS [27]. They reported larger plaque burden (>76%), smaller fibrous cap thickness (<44 μm), and smaller lumen area (<2.6 mm^2) as predictors of culprit plaque in ACS [27].

On the other hand, the merit of predicting ACS based on plaque morphology is questioned by data on the temporal instability of plaque characteristics [28]. Kubo et al. studied 216 non-culprit lesions in 99 patients with stable ischemic heart disease using virtual histology (VH) intravascular ultrasound (VH-IVUS) at baseline and after 12 months follow-up [28]. Three fourths of TCFAs identified on baseline VH-IVUS healed and changed their morphology to either thick cap or fibrotic atheroma on follow-up imaging [28]. Conversely, plaques with intimal thickening and those with thick cap at baseline progressed to TCFA after only 1-year follow-up [28]. Interestingly, there was no difference in the baseline VH-IVUS composition and characterization of TCFA, which subsequently healed, versus those which did not [28]. Another study from the same group evaluated dynamic progression of plaque morphology in patients with ST-segment-elevation myocardial infarction (STEMI) from HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial using baseline and follow-up VH-IVUS [29]. They reported much higher prevalence of TCFA among patients with ST-elevation myocardial infarction at baseline and a significant decrease in minimal luminal area and increase in necrotic core without signs of healing at the end of a 13-month follow-up [29]. Both studies suggest that CAD is an active and constantly changing process, hindering prediction of ACS on the grounds of baseline atherosclerotic plaque imaging. Lastly, plaque erosions are currently not reliable detected by in vivo imaging nor are plaque characteristic prone to erosions. Given that plaque erosions are implicated in 25–35% of ACS cases [12], it is clear that the quest for imaging the vulnerable plaque to reliably identifying patients at risk of ensuing ACS is an elusive concept at present.

Pathophysiology of ACS: a Perfect Storm Scenario

An important fact to consider for the quest of predicting acute coronary events based on identifying vulnerable plaques is the evidence that most plaque erosion or ruptures do *not* lead to clinical events. Arbab-Zadeh and Fuster summarized data from pathology and imaging studies demonstrating that 10–20% of non-culprit lesions reveal evidence of prior rupture *without* associated symptoms [30•]. Pathology studies established that plaque rupture and subsequent healing indeed represent an important, possible integral mechanism for plaque growth [31]. Given that many prior ruptures cannot be detected after complete healing and considering the very large number of non-culprit plaques (as evident by the high prevalence of asymptomatic coronary atherosclerotic disease in our population), it is clear that only a small fraction of plaque ruptures actually leads to ACS [30•, 31]. Thus, even if we identified with great accuracy plaques that will rupture, we are unlikely to prevent events as most of them rupture clinically silently anyway. Available evidence suggests that acute coronary syndromes are not caused by a single factor, but rather occur due to a constellation of numerous factors and conditions leading to "perfect storm" scenario [31]. The convergence of key processes, such as presence of a nidus for thrombosis (plaque rupture, erosion, or calcified nodule), acute vascular inflammation, and a thrombosis conducive milieu *at the time* of plaque disruption, may indeed lead to symptomatic luminal thrombosis [31]. However, the temporal variability among the occurrence of these key processes makes it exceedingly improbable to accurately predicting their convergence [31]. The concept of a perfect storm scenario for the development of ACS is supported by the near linear relationship between the coronary atherosclerotic plaque burden and the risk of cardiovascular events [32]. The more plaques are present, the greater is the probability that one of the associated ruptures (as they inevitably occur) will coincide with a thrombosis conducive condition leading to clinical manifestation. On the other hand, there is evidence of increased probability of ACS even in patients with mild CAD if they have a pro-thrombotic milieu (e.g., hypercoagulable states, inflammation, environmental factors) [33].

Not the presence of a single vulnerable plaque but the presence of many, particularly actively growing plaques along with risk factors for a pro-thrombotic milieu will increase risk of ACS [30•, 31, 34, 35]. Expectedly therefore, risk is lowered by medical management aimed at slowing the progression of CAD and altering the pro-thrombotic milieu via platelet inhibition and risk factor optimization [36, 37]. Conversely, treatment approach focusing on treating "high-risk lesions" failed to reveal any substantive benefits in patients with stable CAD [38, 39].

Potential Merit of Atherosclerosis Imaging

The foregoing supports the role of identifying the presence, extent, and severity of CAD for estimating the risk of future adverse cardiovascular events [30•]. Fortunately, recent advancements in the fields of CT and magnetic resonance imaging (MRI) allow comprehensive CAD assessment non-invasively [40]. In addition, atherosclerosis imaging of the peripheral arterial system has shown to aid in risk assessment. The BioImage Study (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population) has revealed that detection of subclinical carotid or coronary

atherosclerosis using a comprehensive imaging approach using coronary artery calcium score and carotid ultrasound improves the risk prediction for adverse events compared with conventional risk factors [41]. Comprehensive assessment of coronary atherosclerotic plaque burden in patients using computed tomography coronary angiography (CTA) has recently been shown to be feasible and effective [42, 43]. Several studies have shown good correlation between CTA- and IVUS-derived estimations of plaque burden [44]. Nevertheless, plaque burden assessment by CTA remains technically challenging due to the modest tissue contrast at the vascular borders. Given these limitations, several semi-quantitative methods have been developed to estimate coronary atherosclerotic disease burden by CTA [45, 46]. It is conceivable that such semi-quantitative methods provide sufficient discrimination for effective risk stratification in populations. Our most commonly employed method of risk stratification in clinical practice, i.e., describing the number of coronary arteries with obstructive CAD, indeed correlates well for patient outcome with a more granular assessment of disease burden [47]. Non-contrast CT studies using coronary artery calcium scanning—reflecting burden of calcified atherosclerotic disease—have been shown as effective as traditional stenosis assessment for predicting adverse cardiovascular outcomes in symptomatic patients [48]. Recently, there is increasing awareness of the presence and extent of *non-obstructive* CAD for patient outcome. Accordingly, Arbab-Zadeh and Fuster proposed a revision of our diagnostic criteria for CAD to encompass patients with non-obstructive CAD in the disease spectrum [49•]. In addition to baseline plaque burden assessment, evaluation for plaque progression (or regression) is likely to improve risk stratification in patients [50]. Motoyama et al. showed that plaque progression by follow-up CTA was the most powerful predictor of ACS—notably beyond high-risk plaque features, which also appeared predictive but were not adjusted for atherosclerotic disease burden [51]. Atherosclerotic plaque features associated with high metabolic activity at baseline may correlate with disease progression and thus also with risk prediction beyond that provided by the disease burden. As such, the search for the vulnerable plaque will continue but the focus may shift to markers of vascular inflammation.

Conclusions

At present, there is no conclusive evidence that identifying a vulnerable plaque in patients improves risk assessment for the occurrence of myocardial infarction or death compared to simply evaluating the extent and severity of coronary artery disease. Rupture or erosion of most coronary atherosclerotic plaques occurs without associated clinical syndromes, thus reducing the effectiveness of identifying rupture prone plaques for the purpose of risk prediction. On the other hand, the presence and extent of coronary atherosclerotic plaque burden and its metabolic activity strongly correlate with patient outcome and, therefore, their assessment should be our focus for risk stratification along with consideration of traditional risk factors. It remains to be determined if characterization of individual plaque features can meaningfully add to our current risk assessment.

Compliance with Ethical Standards

Conflict of Interest Both authors declare that they have no conflict of interest.

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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