The Myth of "The Vulnerable Plaque": Transitioning from a Focus on Individual Lesions to Atherosclerotic Disease Burden for Coronary Artery Disease Risk Assessment

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Abstract

The cardiovascular science community has pursued the quest to identify vulnerable atherosclerotic plaque in patients for decades, hoping to prevent acute coronary events. However, despite major advancements in imaging technology that allow visualization of rupture-prone plaques, clinical studies have not demonstrated improved risk prediction compared to traditional approaches. Considering the complex relationship between plaque rupture and acute coronary event risk suggested by pathology studies and confirmed by clinical investigations, these results are not surprising. This review summarizes the evidence supporting a multifaceted hypothesis of the natural history of atherosclerotic plaque rupture. Managing patients at risk of suffering acute coronary events mandates a greater focus on the atherosclerotic disease burden, rather than on features of individual plaques.

Keywords

Introduction

Cardiovascular atherosclerotic disease is the leading cause of death in Western industrialized nations and in developing countries (1). Strategies to prevent acute coronary events and their sequelae are among our most important public health priorities (2). Identifying patients at increased risk of suffering an acute coronary event who may benefit from intensified preventative measures is a major, ongoing challenge (2). Numerous factors (e.g.,

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dyslipidemia, diabetes, and others), are associated with increased rates of adverse events; however, their hazard rates are too small for accurate individual risk assessments (3). The DIAD trial revealed that after 4.8 years of follow-up, 97% of asymptomatic patients with diabetes mellitus remained free of myocardial infarction and cardiac death (4). Even when combined as comprehensive risk scores (e.g., by the Framingham study (5)), predictive accuracy is insufficient for adequate individual risk assessments, leading to substantial overtreatment and undertreatment, with associated morbidity and societal costs (6).

The mechanisms leading to adverse events from atherosclerotic disease are clearly more complex than initially assumed, explaining our difficulties in accurately predicting events in individuals (7, 8). In addition to the presence, extent, and metabolic activity of atherosclerotic disease, individual adaptations and responses to thrombogenic stimulation from altered vascular function are critical for determining the risk of acute coronary events (7, 9). Despite a consensus on the complexity of acute coronary event risk evaluation and the necessity for comprehensive patient assessment (10,11), recent efforts to identify high-risk patients focus on using advanced imaging methods to detect single "vulnerable" atherosclerotic plaques (12). This narrow focus neglects the complexity of the processes leading to risk and lacks supporting evidence. This review summarizes the shift from conceptualizing acute coronary event risk as a simple cause-and-effect principle centered on high-risk plaques to a complex model involving numerous factors.

"The Vulnerable Plaque" Concept

Pathology studies demonstrated the common association of acute myocardial infarction with the rupture or erosion of a coronary atherosclerotic plaque (13,14), most frequently a thin-cap fibroatheroma (TCFA), characterized by a large lipid or necrotic core separated from the coronary arterial lumen by a thin membrane cap (15). Thus, identification of TCFAs in humans was assumed to signify a high risk of ensuing acute coronary events, which then might necessitate directed treatment or specific preventative measures (16). Accordingly, enormous efforts have been undertaken to enable identification of TCFAs and other high-risk plaque features in humans. The search term *vulnerable plaque* finds more than 400 *current* National Institutes of Health (NIH) research awards totaling more than $150,000,000 per year (17) and almost 2,000 research papers in the U.S. National Library of Medicine database. While not all of these efforts aim to identify "vulnerable plaques", this topic is clearly central to many investigations involving large amounts of research dollars. Industry has also been keenly interested in developing technologies for visualization of "vulnerable plaques", with progression of several catheter-based inventions, notably virtual histology intravascular ultrasound, thermography, infrared spectroscopy, palpography, and optical coherence tomography to preclinical or clinical stages (12,18).

Limitations of Studies Supporting the High-Risk Atherosclerotic Plaque Concept

A number of clinical investigations reported using various imaging tools to identify high-risk atherosclerotic plaque features in order to predict an increased risk of adverse events. A large, prospective clinical study, PROSPECT, investigated the rates of adverse cardiac

events according to types of coronary atherosclerotic plaque in more than 600 high-risk patients studied with virtual histology intravascular ultrasound (19). While 596 TCFAs were identified, only repeat hospitalization for chest pain was associated with events. This was expected, given the typically larger lumen encroachment of TCFAs compared to pathological intimal thickening (the prevalent type of lesion in the study). However, the risk of myocardial infarction or sudden cardiac death related to these lesions was very low (Figure 1). A similar study using virtual histology intravascular ultrasound (VIVA) reported nearly identical findings (20). Studies using optical coherence tomography (OCT) revealed greatly detailed plaque characteristics in patients with acute coronary syndrome and other at-risk populations (21). Similar to the information provided by intravascular ultrasound (IVUS), OCT studies suggest that a larger lesion plaque burden might indicate an increased risk of acute coronary events (22). Noninvasive imaging studies of the coronary arteries using CT angiography reported increased rates of acute coronary syndromes in patients with low-attenuation plaques (presumably high in lipid content) with external remodeling compared to those without such plaques (23–25). Puchner et al. recently reported independent prediction of acute coronary syndrome using CT to identify similar high-risk characteristics in patients presenting with *acute* chest pain (26). Finally, plaque hemorrhage, assessed by magnetic resonance imaging, has been implicated in poor outcomes of patients with cerebrovascular disease (27,28). However, all of these studies claiming independent risk prediction of certain plaque features share the fundamental limitation that the atherosclerotic disease burden was not considered as a potential confounder. These "high-risk" features are conceivably mere markers of more extensive and/or active atherosclerotic disease compared to the control group. Given the overwhelming evidence for disease burden as a powerful predictor of outcome, any additional risk features should be assessed against it before we assume independent risk prediction. Therefore, despite promising results from a number of clinical studies, there is no conclusive evidence for truly independent risk prediction associated with high-risk plaque features. High-risk features may still be valuable as markers for disease burden or activity; however, such value has not been established.

Evidence Diminishing the Significance of Identifying "High-Risk" Plaques

Despite our ability to identify atherosclerotic lesions that exhibit vulnerable characteristics using various imaging tools, clinical studies have failed to demonstrate meaningful clinical utility for plaque imaging. These negative results are explained by the numerous pathological and clinical investigations demonstrating that many (if not most) plaques rupture *without* clinical syndromes (22,29–38). The percentage of patients with subclinical plaque ruptures varies with their risk profile and the sensitivity of assessment methods, ranging from 4% to 79% (Table 1). Plaque rupture and its healing are frequently clinically silent, but lead to progressive lumen obstruction (39,40). In lesions with advanced lumen narrowing (>50% stenosis), histopathology almost invariably reveals 1 or more healed subclinical plaque ruptures (39–41). Because healed plaque ruptures can only be detected by pathology or imaging within a certain time frame after the initial plaque disruption, the true rate of asymptomatic plaque ruptures is probably underestimated (40). In most individuals with advanced atheroma, plaque rupture and subsequent healing have already occurred (40). Pathology studies show that approximately 10% of the subclinical U.S. adult population

exhibits advanced coronary atheroma (42), thus, it is reasonable to assume that many millions of persons unknowingly experience plaque ruptures each year. Several longitudinal imaging studies in humans demonstrate that plaque morphology changes over a few months, gaining or losing "vulnerable" characteristics (43–45). Using IVUS, Kubo et al. found that 75% of TCFAs transition to *thick*-cap fibroatheromas or fibrotic plaques within a 12-month interval, presumably secondary to rupture and healing (Figure 2). None of these patients experienced an event during this period, providing further evidence of frequent subclinical plaque alterations. A recent study used OCT to confirm the dynamic nature of coronary atherosclerotic disease, demonstrating that TCFAs in various stages of development are highly prevalent in patients with coronary atherosclerotic disease (46). In patients with acute coronary syndrome, plaque ruptures are frequently found apart from the culprit lesions, indicating that vulnerability is disseminated throughout the coronary tree (41). This suggests that detection of a *state* of vulnerability in a patient (e.g., widespread inflammation) is more important than detection of individual *sites* of vulnerability. The emerging picture of acute coronary event pathophysiology suggests a widespread, systemic condition with great unpredictability as to which particular lesion will be associated with clinically-significant vascular thrombosis (47). While plaque ruptures and erosions are, indeed, responsible for most culprit lesions in patients with acute events, because the frequency of *subclinical* plaque ruptures is vastly underestimated, the assumption that identifying lesions prone to rupture will prevent acute coronary events was unrealistic. Of the many plaque ruptures occurring in patients with atherosclerotic disease, very few will trigger symptomatic events, rendering it exceedingly difficult to predict adverse outcomes associated with particular lesions. Identifying a single TCFA or other "high-risk plaque", without considering other clinical or imaging characteristics, is unlikely to be of incremental benefit for risk prediction over established factors (e.g., extent and distribution of atherosclerotic plaque burden), because of the low risk associated with a given *individual* plaque and the temporal relationship of its vulnerable characteristics.

Current Paradigm of Acute Coronary Event Pathophysiology

Over the past few decades, clinical and laboratory investigations have led to a more complex concept of the pathophysiology of acute coronary events, involving numerous processes, many with poorly-understood interactions (7,8). While the occurrence of acute coronary events typically requires alterations of coronary atherosclerotic plaques (rupture or erosion), a thrombosis-promoting milieu is necessary to allow a clinically significant decrease in coronary blood flow and associated myocardial ischemia (7,9). Such a setting appears to result from an unfortunate constellation of prothrombotic features, for example, in patients with increased inflammatory activity and systemic or local suppression of fibrinolytic performance, an extraordinarily large stimulus for thrombosis, vasoconstriction, and/or others (7). The respective contributions of these factors (some hereditary, some environmental) and their temporal relationships necessary to trigger clinically meaningful vascular thrombosis are unknown. Factors favoring thrombosis need to be collectively sufficient to tilt the scale away from localized thrombus and towards extensive vascular thrombosis (Central Illustration). Because numerous factors influence the performance of the coagulation system at any given point in time, acute coronary events may arise as result

of a "perfect storm" scenario, in which plaque disruption occurs in a specific, thrombosis-promoting setting (7). The risk of an acute coronary event equals the probability of plaque rupture/erosion coinciding with vascular thrombosis-promoting conditions that cannot contain the thrombus in the vascular wall. Frequent plaque ruptures, as with a large, metabolically active atherosclerotic disease burden, increase the chance that a plaque rupture coincides with a thrombosis-conducive setting. Accordingly, the strongest predictors of adverse events are the magnitude and activity of the coronary atherosclerotic plaque burden and the number of risk factors for a prothrombotic milieu, a concept supported by many clinical studies and epidemiologic data (3,5,48–50).

Lesion Focused Versus Disease Burden for Risk Assessment and Management

Numerous clinical studies using conventional invasive coronary angiography, IVUS, and cardiac CT (8,48,51) confirm the strong relationship between atherosclerotic disease burden and risk of adverse events. Despite capturing only calcified atherosclerotic disease, when compared directly, coronary calcium scoring was equivalent to traditional stenosis assessment for predicting mortality and myocardial infarction in asymptomatic patients (52). Using a comprehensive imaging approach in several vascular beds, the BIOIMAGE study recently revealed a high prevalence of atherosclerotic disease in individuals categorized as high-risk for cardiovascular events based on clinical predictors (53). Halting coronary atherosclerotic disease progression and/or altering the vascular thrombosis-promoting milieu via platelet inhibition and risk factor interdiction are approaches proven to lower myocardial infarction and death rates (54–56). Conversely, meta-analyses have not demonstrated reduced rates of myocardial infarction or death with lesion-based treatment (i.e., percutaneous coronary intervention) compared to medical therapy in patients with stable coronary artery disease (57,58). Contradicting some earlier reports (59–62), no benefit was shown, even when selecting patients with hemodynamically significant stenoses. These results confirm that risk is most strongly conveyed by the extent of coronary artery disease, but not necessarily by individual lesions, even when highly obstructive. This supports the controversial idea that severe coronary artery stenoses are no greater risk for triggering acute coronary events than mild lesions (63). Earlier angiographic studies suggested that most myocardial infarctions arise from mild coronary artery stenoses (64,65), but recent data question this paradigm (66,67). Thrombus material accumulates over several days following a plaque disruption, which may not allow lesion size and a partly organized thrombus to be accurately distinguished (66). Pathology studies in patients who died suddenly found culprit lesions to have an average diameter stenosis of approximately 50%, with no clear relationship between stenosis severity and risk of death (68,69). Conversely, acute coronary death rarely results from lesions with <30% lumen stenosis (66,69). Thus, a certain local plaque volume appears necessary to trigger vascular thrombosis. However, given the lack of benefit with coronary stenting, as well as the large number of obstructive lesions found by imaging and autopsy in patients without symptoms of acute coronary events, stenosis severity is unlikely to substantially alter such risk beyond a particular threshold. Patients with high-grade coronary artery stenoses may conceivably carry an increased risk of suffering myocardial infarction and death because these lesions are markers for advanced

atherosclerotic disease in the coronary tree (7). Consistent with this notion, nonobstructive and obstructive coronary artery disease are associated with similar risks of myocardial infarction and death if the former affects a larger number of coronary arterial segments (Figure 3)(70). Overall, strong evidence supports addressing the extent and activity of the atherosclerotic burden and thrombosis-promoting risk factors for improved patient outcomes, but there is no conclusive evidence of incremental risk reduction with lesion-specific treatment.

Areas of Uncertainty: Influence of Study Population

The atherosclerotic disease burden is a powerful predictor of outcomes for patients without prior history of coronary artery disease, facilitated by the ease of coronary calcium scanning, which approximates the total coronary atherosclerotic disease volume (71). However, it is infrequently performed in patients with established coronary artery disease; thus, in this population, plaque burden data are more limited. Risk characteristics and the need for assessment may conceivably differ in patients with established coronary artery disease compared with those with a history of acute coronary syndrome. Aside from calcium scanning, plaque burden assessment is technically difficult and most available data were from IVUS imaging. Atherosclerotic plaque burden assessment using CT angiography has recently become feasible, but long-term outcome data are not yet available (72). Aggregate data from IVUS-derived plaque burden assessment reveal its strong predictive power for outcomes in patients with established coronary artery disease (73). Conventional angiography data for atherosclerotic disease burden are similarly predictive of patient outcome and superior to myocardial ischemia testing in an analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study (74). Thus, the risk associated with plaque burden applies to both asymptomatic individuals without prior cardiac events and those with established, stable coronary artery disease. Whether lesion-based treatment (aside from the culprit lesion) is beneficial in patients with acute coronary syndrome is unclear. Two recent small clinical studies suggested reduced rates of myocardial infarction and death following percutaneous coronary intervention of nonculprit lesions in patients with ST-elevation myocardial infarction (75,76), in stark contrast to large, aggregate data suggesting the opposite (77). In addition to concerns about the effect of chance, given the small numbers of events in these 2 studies, the contributions of event allocation (e.g., differentiating spontaneous and periprocedural events) and varying levels of expertise at the study centers to these results remain unclear. PROSPECT, conducted in patients with acute coronary syndrome, found low risk of myocardial infarction and death associated with nonculprit lesions within 3 years of follow-up (19). A large clinical study, COMPLETE, is underway to conclusively address the question of benefit of stenting nonculprit lesions in patients with ST-elevation myocardial infarction (78).

Is there a Role for Individual Plaque Imaging?

Coronary artery imaging has provided insights into numerous lesion characteristics, but we have yet to identify which are useful for guiding management. Changing patterns of lesion characteristics, resulting from widespread use of lipid-modifying medications, pose an additional challenge (79). There are promising data for characterizing coronary arterial

lesions prior to percutaneous interventions (80,81). Heavily calcified lesions adversely affect the outcome of coronary artery revascularization and imaging data may help weigh treatment options (82–83). Similarly, knowledge of complex bifurcation lesions prior to cardiac catheterization may avoid high-risk interventions (80,81). Plaque imaging also may elucidate the effects of drugs on atherosclerotic disease (84). Individual plaque features may have particular significance in specific settings: for example, a TCFA may have different implications in patients with or without known susceptibility to vascular thrombosis. Thus, integration of lesion characteristics with risk factors may be valuable. Currently unknown features of atherosclerotic plaque may conceivably independently herald poor outcome. Advanced imaging techniques (e.g., molecular imaging), may elucidate such features and allow further insights into mechanisms of acute coronary event pathophysiology (85). To determine truly independent risk prediction, any plaque assessment should be measured against the predictive power of atherosclerotic burden and its metabolic activity.

Implications for Future Investigations

While general morphologic patterns of atherosclerotic disease influence the probability of acute coronary syndromes, they are clearly modified by individual characteristics. Pathology and IVUS studies show that most U.S. adults above 50 years of age have evidence of coronary atherosclerotic disease, but only a minority will suffer acute events (42,86). Furthermore, the patterns and morphologic features of atherosclerotic disease appear similar among populations, suggesting that the individual's response is critical for determining the probability of events. Traditional risk factors for coronary artery disease (e.g., diabetes, smoking, dyslipidemia), and genetic predisposition modify such responses. Several mutations are associated with increased event hazard and individualized risk characterization may soon be available (87–89).

We need a better understanding of which combination of imaging information and risk factors yields the most accurate individual risk prediction. Research is needed to investigate mechanisms influencing the coagulation system's response to various internal and external modifiers, both locally and systemically. Specifically, we need to understand and potentially to predict the response of the coagulation system to stimuli occurring with atherosclerotic plaque alterations. Variability in the coagulation system's performance depends on numerous hormonal, dietary, and environmental influences, hampering our ability to predict its function at a given time, for example, when plaque ruptures (90–92). Thus, we must strive for comprehensive risk assessment that *integrates* specific information on the atherosclerotic plaque burden and systemic factors that increase the risk of disease activity and vascular thrombosis, and is tailored to specific patient populations and individuals. This would enable effective, efficient triaging of patients into treatment categories ranging from continued risk factor control to coronary arterial revascularization.

Conclusions

Despite major advancements in coronary artery imaging and identification of atherosclerotic lesion morphology associated with rupture, there is no conclusive evidence that individual plaque assessment better predicts acute coronary event risk than established risk factors,

such as the extent and severity of coronary artery disease. Pathology and clinical studies consistently demonstrate that atherosclerotic plaques rupture without clinical symptoms much more frequently than is widely acknowledged, challenging the notion of a close association between plaque rupture and clinical event. Conversely, the atherosclerotic disease burden is a consistent, strong predictor of adverse cardiovascular events and deserves greater attention. Current data suggest that, rather than focusing on individual coronary arterial lesions, we need a comprehensive, integrative approach for identifying and managing patients at risk of suffering adverse cardiovascular events.

Acknowledgments

Abbreviations

CT	computed tomography
IVUS	intravascular ultrasound
OCT	optical coherence tomography
TCFA	thin-cap fibroatheroma

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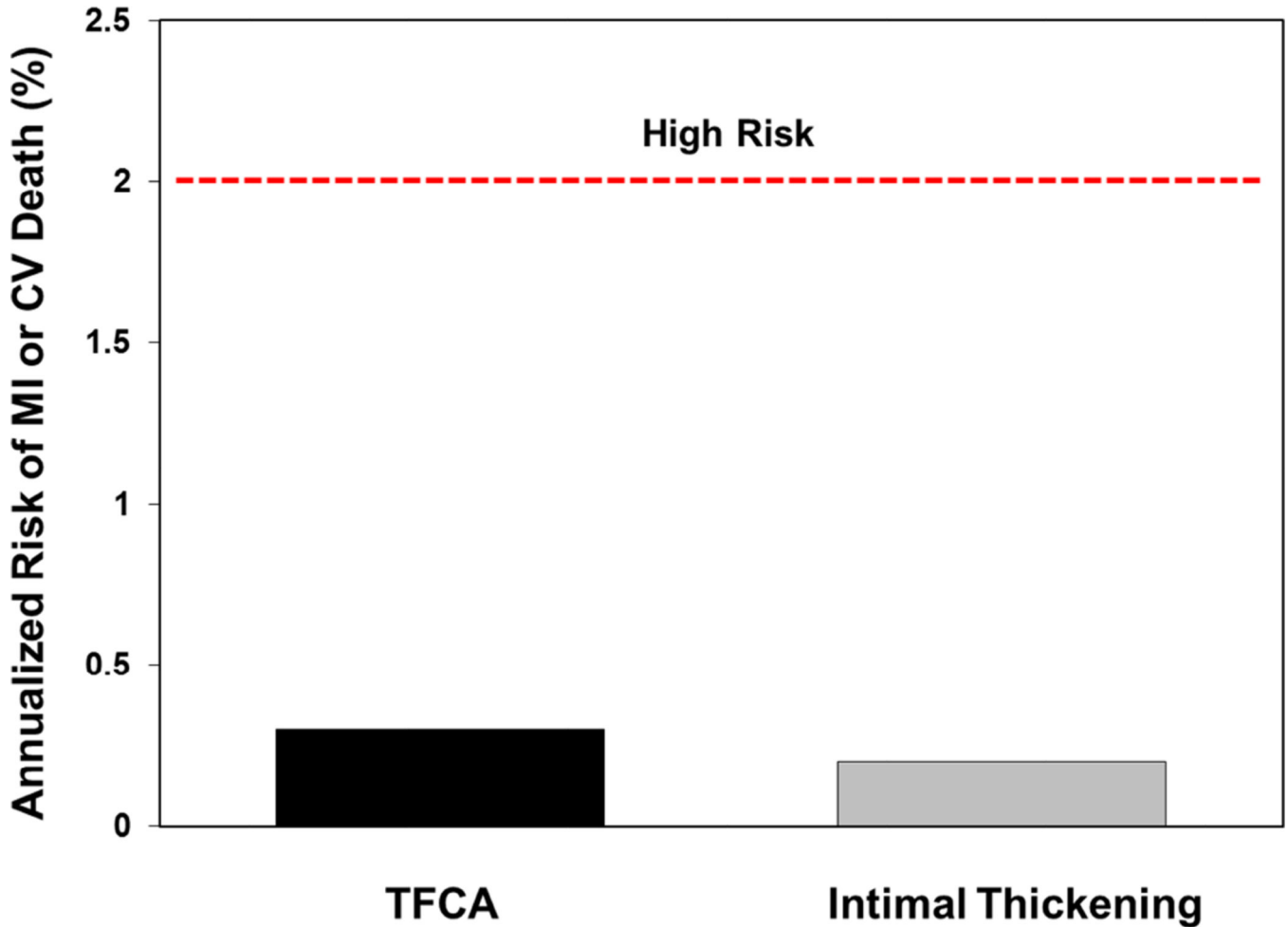
Figure 1. Risk of MI/Death Associated With Individual Plaques in the PROSPECT Study
Maximum annualized risks (%) of MI or CV death associated with individual coronary
atherosclerotic plaques identified at baseline by virtual histology intravascular ultrasound in
the PROSPECT study are shown (18). The rates are on the basis of the occurrence of 6
events (6 myocardial infarctions and 0 deaths) after 3.4 years of follow-up among 1,005
coronary arterial sites with pathological intimal thickening and 595 TCFAs, assuming all
events were caused by the respective plaque type, thus representing the worst-case scenario.
Considering equal risk among the 3,160 plaques detected at baseline (best-case scenario),
the event rate associated with each plaque would be only 0.06%/year. The risk of MI or
death associated with individual TCFA or vulnerable plaques is much smaller than what is
conventionally considered high-risk, even when maximal risk is assumed. CV =
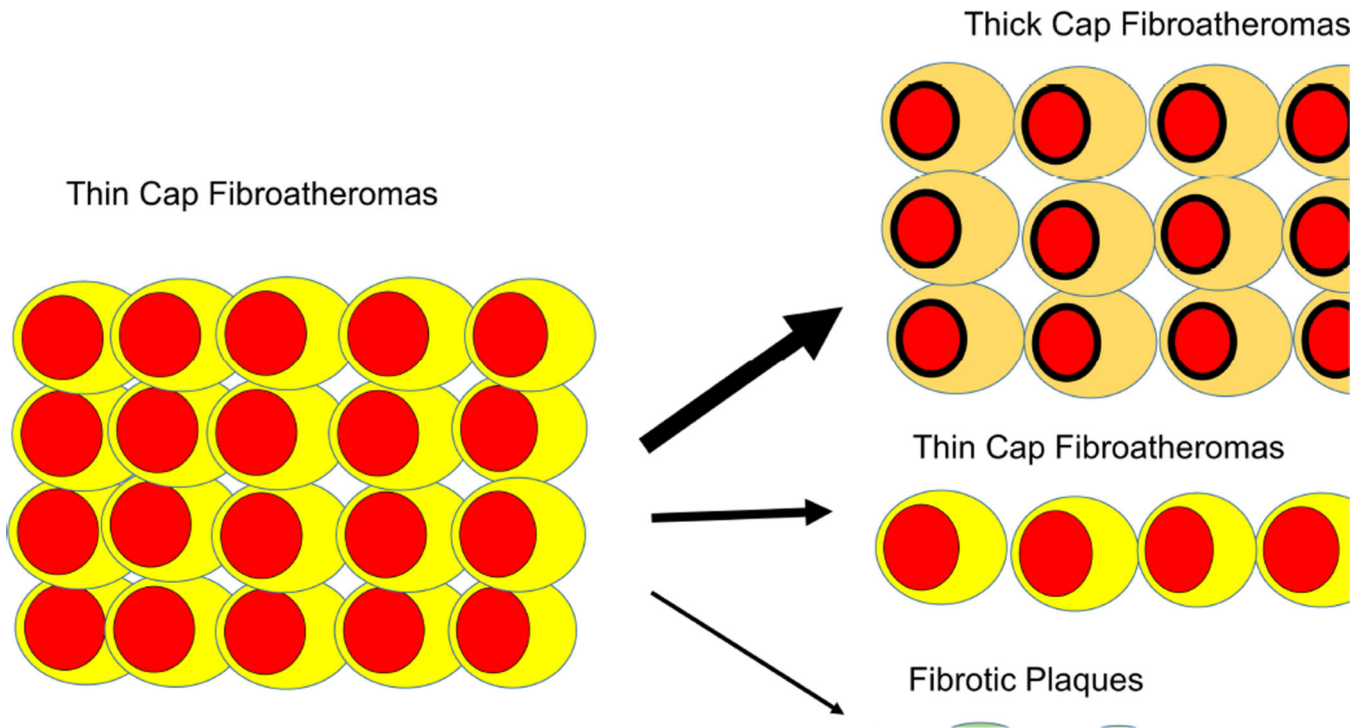cardiovascular; MI = myocardial infarction; TCFA = thin-cap fibroatheroma.

Figure 2. Changes in TCFAs During 12 Months Follow-Up
Changes in TFCAs observed with virtual histology intravascular ultrasound 12 months after
baseline imaging. Of 20 TFCAs, only 5 remained unchanged while 15 (75%) lost vulnerable
characteristics and revealed thickening of the fibrous cap or transformed into fibrous
plaques. The data (Kubo et al. (43)) demonstrate high metabolic activity in atherosclerotic
lesions and the short-lived nature of vulnerable plaque characteristics. None of the 99
patients experienced any events during follow up; thus many of the observed changes were
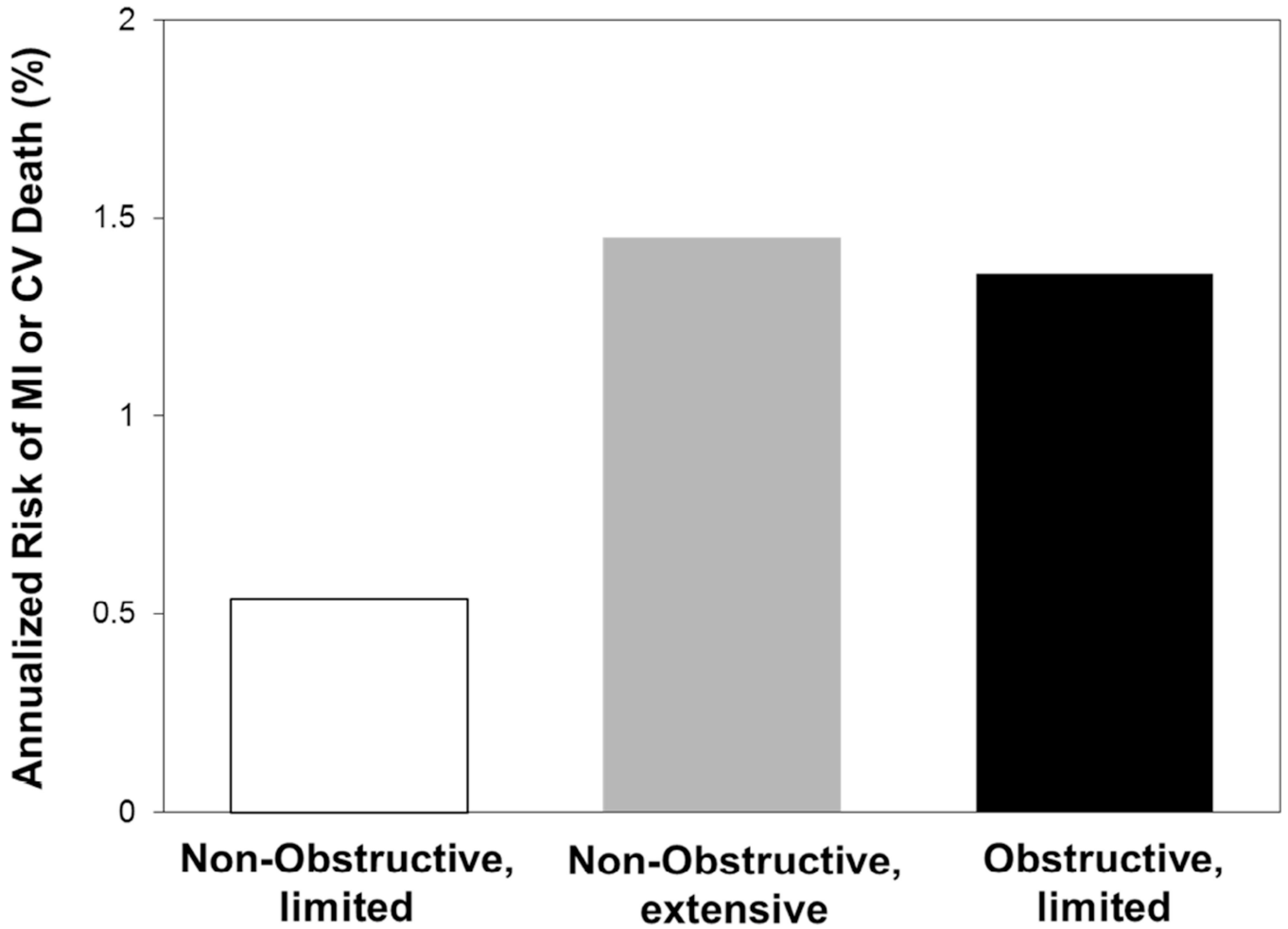likely the result of subclinical plaque ruptures. Abbreviations as in Figure 1.

Figure 3. Risk from Non-Obstructive Versus Obstructive Coronary Artery Disease
Annualized risk (%) of MI or CV death in 3,242 patients followed for a median of 3.6 years
after a baseline CT coronary angiogram, according to the extent and severity of coronary
artery disease (70). Risk is low in patients with nonobstructive disease (<50% stenosis)
involving 4 or fewer coronary artery segments (limited disease). Conversely, the risk is
similarly high in patients with nonobstructive disease if more than 4 segments are affected
(extensive disease) compared to patients with obstructive disease (50% stenosis). Modified
from Bittencourt et al. (70). CT = computed tomography. Other abbreviations as in Figure 1.
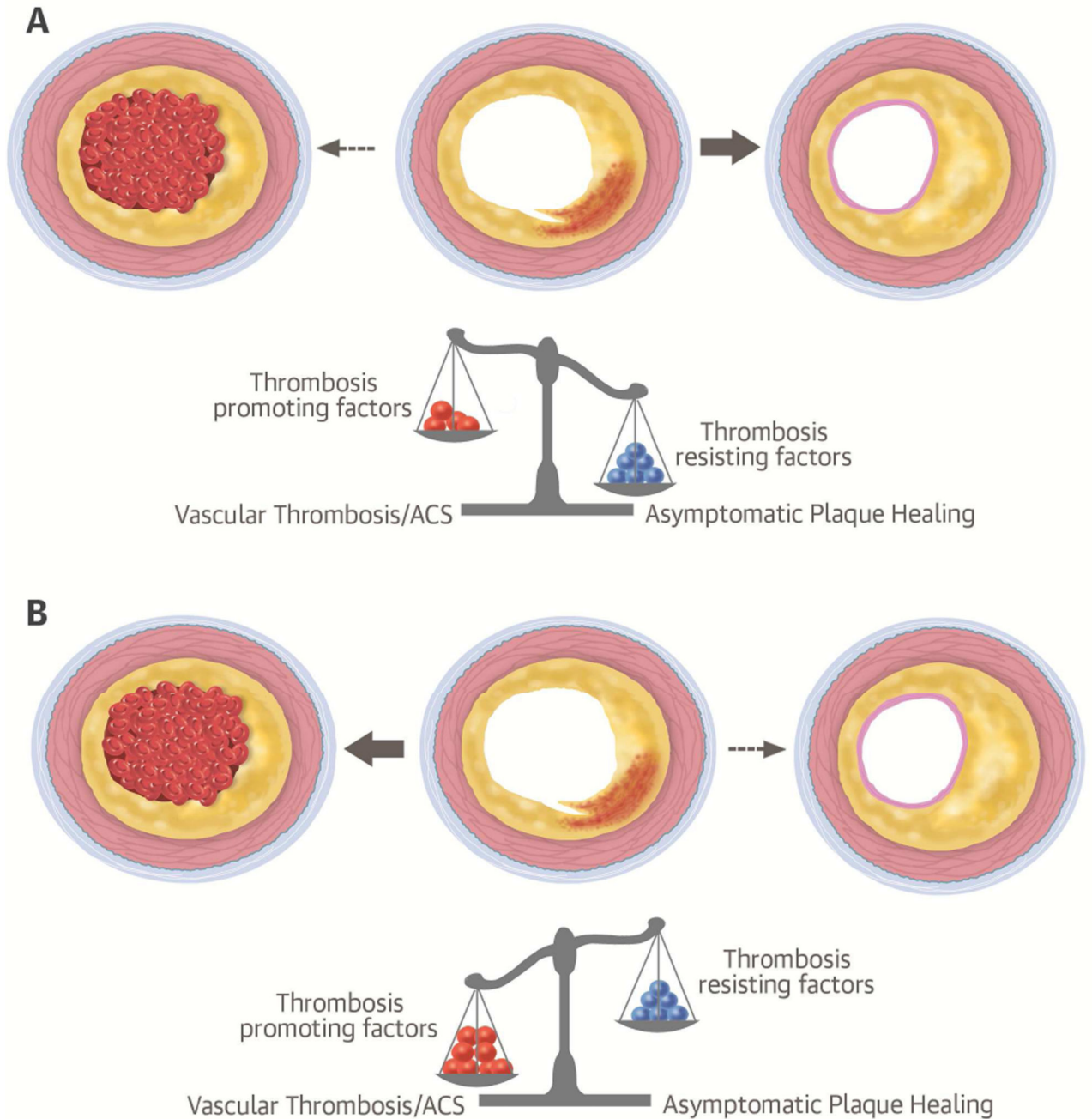
Central Illustration. Fate of Ruptured Coronary Atherosclerotic Plaques According to Thrombotic Milieu

The hypothesized interplay of prothrombotic and thrombosis resisting/containing factors that presumably determine the outcome of a ruptured coronary atherosclerotic plaque is shown. **(A)** In the most common scenario, small thrombus formation associated with plaque rupture is contained and vascular occlusive thrombus is inhibited. **(B)** In the less common scenario of several prothrombotic factors coinciding (e.g., inflammatory state, large lesion plaque burden, vasoconstriction, circadian rheological changes), local thrombosis associated with

plaque rupture cannot be contained and clinically significant vascular thrombosis occurs, triggering an acute coronary syndrome (ACS). The constellation of factors leading to these different outcomes is unknown.

Table 1

Prevalence of *Subclinical* Coronary Atherosclerotic Plaque Ruptures (%) in Patients With Stable Coronary Heart Disease or Healthy Controls and in Individuals With Acute Coronary Syndromes

Study	Mode of Assessment	Number of Stable CHD Patients or Controls[*]	Nonculprit Plaque Ruptures (%)	Number of ACS Patients	Nonculprit Plaque Ruptures (%)
Arbustini et al. (29)	Pathology	77[*]	17	106	58
Cheruvu et al. (37)	Pathology	13[*]	31	33	45
Riofol et al. (40)	IVUS	-	-	24	79
Kotani et al. (36)	IVUS	48	6	38	11
Schoenhagen et al. (35)	IVUS	92	4	105	19
Hong et al. (34)	IVUS	113	5	122	17
Tanaka et al. (28)	IVUS	-	-	45	24
Takano et al. (33)	Angioscopy	-	-	327	9
Tanaka et al. (32)	OCT	-	-	45	24
Tian et al. (21)	OCT	-	-	82	10
Shimamura et al. (31)	OCT	191	17	-	-
Total N		**444**		**927**	
Median		**11.5**		**21.5**	

Multiple asymptomatic plaque ruptures are more frequently found in ACS patients than in individuals with stable CHD or healthy controls, indicating the systemic inflammatory state in the coronary arteries with acute events. ACS = acute coronary syndrome; CHD = coronary heart disease; IVUS = intravascular ultrasound; OCT = optical coherence tomography.

[*] Indicates healthy controls.