Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 12, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.05.088

VIEWPOINT AND COMMENTARY

High-Risk Coronary Atheroma

The Interplay Between Ischemia, Plaque Burden, and Disease Progression

Rishi Puri, MB, BS, Stephen J. Nicholls, MB, BS, PhD, Stephen G. Ellis, MD, E. Murat Tuzcu, MD, Samir R. Kapadia, MD

Cleveland, Ohio

Necropsy studies have outlined the morphological characteristics of high-risk, or "vulnerable," coronary plaque segments, demonstrating the presence of inflammatory infiltrate and various compositional elements in patients who succumbed to fatal intracoronary thrombosis. However, accumulating evidence in vivo relates the overall burden of atherosclerosis, its rate of progression, and its subsequent ischemic potential with the risk for incident clinical events. These observations, coupled with the efficacy of contemporary medical therapies in reducing clinical event rates, have important implications for trial design of future human in vivo evaluations of vulnerable coronary plaque. (J Am Coll Cardiol 2014;63:1134–40) © 2014 by the American College of Cardiology Foundation

In 1989, Muller et al. (1) described non–flow-limiting coronary stenoses that had a propensity to rupture and cause acute myocardial infarctions (AMI) as "vulnerable" plaques. This definition was formally revised by an international panel of experts in 2004, to include plaques prone to rupture, erosion, or containing a calcified nodule, particularly in a patient deemed systemically "vulnerable" (2). Nearly 25 years later, the ability to consistently identify plaque segments that predict incident coronary events remains a challenging task, particularly in the current era of optimal medical therapies that have altered the natural history of coronary atheroma in vivo. More contemporary angiographic evaluations of culprit lesions that resulted in AMI have demonstrated the likelihood of rapid lesion progression in the ensuing months before the occurrence of AMI (3). Accumulating evidence also links ischemic coronary lesions with incident coronary events. Whether AMIs are more likely to immediately arise from within a mildly diseased coronary segment (<50% angiographic stenosis severity) versus a functionally significant, or obstructive (>50% angiographic stenosis severity) lesion at the time of AMI, remains a topic of debate (4).

From the Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio. Dr. Nicholls has received research support from AstraZeneca, Eli Lilly, Amgen, Takeda, Roche, Novartis, Anthera, and Resverlogix; and is a consultant for AstraZeneca, Merck, CSL Behring, Boehringer Ingelheim, Takeda, Roche, Amgen, Omthera, and Reseverlogix. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 5, 2013; revised manuscript received May 10, 2013, accepted May 13, 2013.

Pathological Observations of Lesions Causing Myocardial Infarction and Mechanisms of Plaque Progression

Necropsy studies have taught us that plaque rupture and erosion account for a majority of cases of intracoronary thrombosis and microembolization, respectively, and these studies demonstrated the presence of multiple healed plaque ruptures, with evidence of layering (5,6). Stenosis severity within the majority of lesions containing rupture was recently reported to be >75% cross-sectional area narrowing (7), whereas the mean stenosis severity in culprit lesions with erosions and downstream emboli was 74% (6). In a seminal pathological study using ex vivo arterial perfusion techniques (to achieve optimal lumen dimensions) for better estimating the extent of lumen compromise before tissue fixation, more than 70% of high-grade stenoses displayed prior plaque disruption that presumably triggered enhanced smooth muscle cell proliferation and plaque growth (8). It was thus felt that silent plaque ruptures and healing (with lesion growth) could either be a consequence of high-grade stenoses per se or occur suddenly/episodically in lower-grade lesions, resulting in rapid plaque growth before a myocardial infarction (MI). Either way, silent plaque ruptures form an important component of plaque wound healing in vivo, facilitating plaque progression. This explains the discord between the frequency of observed plaque rupture, symptoms, and clinical events (9,10). Additionally, the process of plaque rupture, healing, and progression towards a high-grade stenosis appears to be phasic rather than linear. The subclinical nature of this process suggests that current attempts to prospectively identify specific morphological features of plaque segments that predispose to future rupture, erosion, and clinical events is likely to be an inefficient process, representing a difficult challenge.

Lesion progression observed with serial coronary angiography appears unpredictable and nonlinear in course (11–14). Mechanisms underlying human coronary atheroma progression presently remain limited to observations made at autopsy. Nevertheless, these studies identified strong links between intraplaque hemorrhage and atheroma progression (15). Lesion progression is thought to occur via expansion of the necrotic core, which in turn culminates in the formation of a more advanced, vulnerable atheroma phenotype, or fibroatheroma. Leaky vasa vasorum, that permeate atherosclerotic plaque, enable erythrocytes and inflammatory cells to extravasate. Erythrocyte membranes thus form a major source of intraplaque lipid deposition and subsequent necrotic core expansion (16). Therefore, imaging technologies that enable detection of intraplaque hemorrhage in vivo may allow us to more reliably predict coronary atheroma at risk for rapid lesion progression, before possible MI.

Coronary Imaging of Lesions Before Causing MI

A series of retrospective angiographic studies from a patient afflicted with AMI identified baseline culprit lesion severity to range from 30% to 45% (17–21). However, common to these studies was the prolonged time period (range 18 to 40 months) between baseline coronary angiography and the sentinel AMI event (Table 1), coupled with limited numbers of patients in each study.

Specific to the setting of AMI, a study by Ojio et al. (22) investigated the unique situation of 20 patients who happened to undergo elective coronary angiography essentially within 1 week (mean time of 3 ± 3 days) before AMI. Ten of these patients underwent coronary angiography for investigation of exertional angina, and were scheduled for elective percutaneous coronary intervention (PCI) of the symptom-causing, obstructive lesion. Five patients were asymptomatic at the time, undergoing surveillance coronary angiography within 3 months of a prior coronary angioplasty for another symptom-producing lesion. Despite an obstructive lesion being found in the nonintervened vessel, given the asymptomatic status of the patient on antiplatelet or anticoagulant therapy, further PCI was not undertaken. Three patients were felt to present with coronary spasm and were treated medically; the remaining 2 patients were asymptomatic but demonstrated electrocardiographic abnormalities, thus warranting coronary angiography. These patients were compared with 20 control patients who underwent coronary angiography 6 to 18 months (mean time of 282 ± 49 days) before AMI. The mean diameter stenosis severity in the group undergoing angiography 3 days pre-AMI was 71 ± 12%. The mean diameter stenosis severity close to 1-year pre-AMI was 30 ± 18%, highlighting the presence of a more advanced lesion as a substrate for AMI in these patients. Studies by Frobert et al. (23), Brown et al. (24), and Manoharan et al. (25) provided further insight into the nature of culprit lesion severity in the AMI setting treated with primary PCI. Acknowledging the confounding presence of intracoronary thrombus leading to a likely overestimation of stenosis severity, most culprit lesions appeared angiographically severe by quantitative analysis. Similarly, acknowledging the possibility of residual thrombus burden, the angiographic severity of culprit lesions immediately after thrombolytic therapy for AMI (with either streptokinase or recombinant tissue-type plasminogen activator), and following an additional 3 weeks of systemic anticoagulation therapy, was >50% in a majority of patients (26). Furthermore, post hoc analyses from the CASS (Coronary Artery Surgery Study) found that lesions with >50% diameter stenosis severity were independently associated with the occurrence of AMI within 3 years (27). At 5 years, the initial

Abbreviations and Acronyms

AMI = acute myocardial infarction
IPH = intraplaque hemorrhage
IVUS = intravascular ultrasound
FFR = fractional flow reserve
PCI = percutaneous coronary intervention
LDL-C = low-density lipoprotein cholesterol
ECG = electrocardiography
MACE = major adverse cardiovascular event(s)

Table 1 Summary of Studies Specifically Evaluating the Relationship Between Baseline Angiographic Lesion Severity and Progression to MI

First Author (Ref. #)	Study Period	Patient Type: n	Baseline % Diameter Stenosis	Interval Group (Days)
Zaman et al. (3)	2003–2010	STEMI: 41	40 ± 24	720 ± 600
Ojio et al. (22)	1991–1997	STEMI group 1: 20	71 ± 12	3 ± 3
		STEMI group 2: 20	30 ± 18	282 ± 49
Ambrose et al. (17)	1987	QWMI: 15	34*	540 (30–2,520)
		NQWMI: 8	80*	990 (90–3,240)
Dacanay et al. (20)	1980–1991	QWMI: 32	44 ± 25	1,200 ± 840
		NQWMI: 38	23 ± 35	1,320 ± 900
Little et al. (18)	1975–1985	29	44 ± 15	690 ± 690
Giroud et al. (19)	1972–1990	92	N/A†	660 (30–2,820)
Hackett et al. (21)	1978–1985	10	30 ± 15	690 (60–1,770)

Values are mean ± SD or median (interquartile range). *SD not mentioned in study. †Mean percent diameter stenosis not reported, represented only as a categorical variable. Adapted and modified with permission from Zaman et al. (3).

NQWMI = non–Q-wave myocardial infarction; QWMI = Q-wave myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

stenosis severity predicted lesion progression (28). To add to this, Zaman et al. (3) recently conducted a time-based analysis to assess the angiographic severity of coronary stenoses leading to an AMI. Similar to earlier conducted studies, 71% of patients analyzed displayed a <50% diameter stenosis when the angiogram was performed several months before the AMI. However, 57% of lesions that were evaluated within 3 months of an AMI had a stenosis severity of >50% (mean diameter stenosis 59 ± 31%).

A substudy from the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial found that patients with AMI were more likely to have had an originally deferred baseline coronary lesion that was >50% in stenosis severity, with the average stenosis severity at time of angiography for subsequent AMI being >70% (29). The only independent predictor of AMI was an initial non-revascularized lesion of >50% in stenosis severity. The median follow-up time of lesions initially found to be >50% stenosis severity was 0.59 years. In the medically treated group, 4% of lesions that were <50% in baseline stenosis severity became culprit lesions for future events, with a median follow-up time of 1.22 years. In the same group, 25% of lesions with a >50% baseline stenosis severity resulted in clinical events (Fig. 1).

Plaque Burden, Plaque Progression, and Clinical Events: What Is the Evidence?

Historical data suggested that coronary stenosis severity measured angiographically is associated with clinical outcomes (30). Intravascular ultrasonography (IVUS) has been pivotal in outlining the true burden of coronary atherosclerosis in vivo. Angiography has known limitations for outlining the true extent of plaque burden (31). Although some culprit lesions responsible for future AMI may appear mild on an angiogram, these lesions invariably contain significant plaque burden, masked by an outward (expansive, or positive) vessel remodeling process, as originally described by Glagov et al. (32), later confirmed using IVUS (33). There is emerging evidence that the baseline burden of atherosclerosis measured on IVUS is associated with future clinical events (34,35). In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, the major imaging predictors of subsequent cardiovascular events included higher baseline plaque burden, smaller lumen size, and the presence of an IVUS-derived thin-cap fibroatheroma (36). Although the mean baseline diameter stenosis severity of the 106 lesions in the PROSPECT study that were responsible for major adverse cardiac events (MACE) was 32%, these lesions progressed to a mean diameter stenosis severity of 65% at the time of AMI, confirming the interval progression of plaques to a critical, obstructive level of stenosis at the time of AMI. These findings were supported by a smaller, similarly designed study (37). Such findings suggest that measures of plaque composition associate with cardiovascular events, in addition to measures of plaque burden (36,37). Second-generation invasive imaging tools of plaque composition may provide further insights into the role of atheroma composition, mediating the natural history of coronary atherosclerosis, response to therapies, and resultant clinical events.

Acknowledging the limitations of angiography in ascertaining the true extent of arterial wall disease, a unique

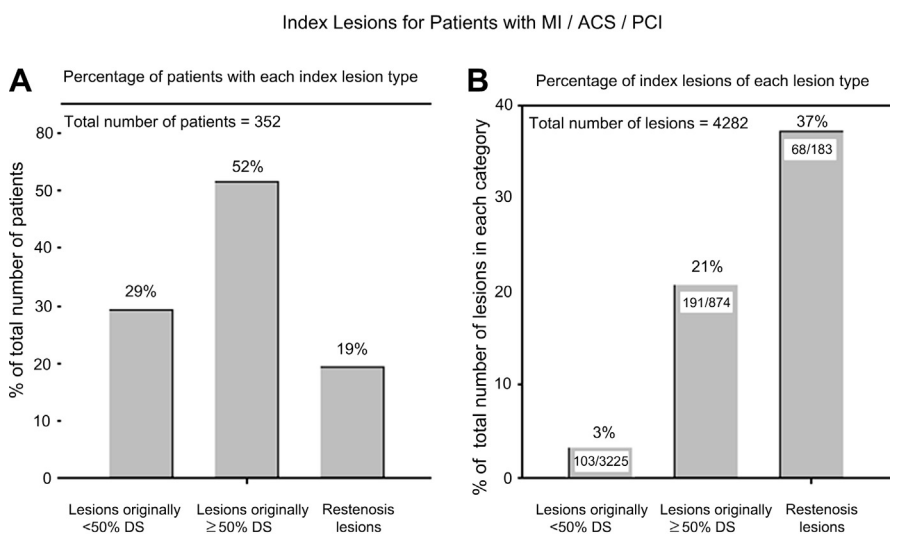

Figure 1 The COURAGE Angiographic Substudy

Index lesion characteristics of patients from the COURAGE trial who developed acute myocardial infarction (AMI) or acute coronary syndrome (ACS), or who needed percutaneous coronary intervention (PCI). ACS = acute coronary syndrome(s); COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DS = diameter stenosis; MI = myocardial infarction. Reproduced with permission from Mancini et al. (29).

analysis undertaken by Yokoya et al. (14) involved analyzing 4 serial coronary angiograms performed at approximately 4-month intervals over a 1-year period in 36 patients. Type 1 lesions were those that displayed marked interval progression (defined as ≥15% diameter stenosis angiographic progression); type 2 lesions were those that showed either slight (5% to 14% diameter stenosis) or no (<5% diameter stenosis) progression. Myocardial infarction, marked disease progression, or angina pectoris occurred in 71% of type 1 lesions. The wealth of serial data of atherosclerosis progression in humans in vivo, however, exists in the setting of clinical trials that utilized serial IVUS to evaluate the efficacy of antiatherosclerotic therapies in nonobstructed (<50% diameter stenosis severity) vessels. Regression of coronary atherosclerosis occurred in patients with on-treatment low-density lipoprotein cholesterol levels below 70 mg/dl (38–40), and in those with modest elevations of high-density lipoprotein cholesterol or via infusing lipid-deplete forms of high-density lipoprotein cholesterol (41,42). This highlights the efficacy of systemic therapies in less advanced, yet potentially vulnerable lesions that may otherwise have demonstrated interval progression to result in a clinical event. More recently, localized endothelial shear stress was found to independently associate with focal plaque progression (43). A pooled analysis of over 4,000 patients in 6 clinical trials who underwent serial coronary IVUS evaluation, identified the rate of epicardial disease progression to independently associate with clinical outcomes (34), largely driven by the need for coronary revascularization. Similar findings were noted in a recent analysis of left main coronary artery segments, whereby plaque progression and constrictive remodeling of the left main segment was associated with incident clinical events (35).

Does Ischemia Equate to a High-Risk Clinical Situation?

Of all the coronary lesions assessed daily in clinical practice, cumulative evidence points to the fact that those lesions conferring the greatest risk for subsequent events, are lesions found to cause ischemia. When fractional flow reserve (FFR) was used to assess the functional significance of a coronary lesion, the chance of mortality or AMI over a 5-year period appeared to be 5-fold higher in patients harboring a functionally significant coronary lesion (evaluated as having an FFR <0.75), as opposed to functionally insignificant lesions (44). These observations with FFR are supported by a wealth of data from noninvasive imaging studies that highlight the adverse prognosis of ischemia-producing lesions in causing AMI or death (45,46). The COURAGE nuclear substudy demonstrated an association between ischemia reduction (by either PCI or medical therapy) and lower long-term rates of death or AMI (47). A separate analysis of COURAGE showed that worsening of ischemia, on serial single-photon emission computed tomography, was also an independent predictor of death or AMI (48).

More recently, the FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2) trial evaluated patients with stable angina and documented coronary disease, with identified lesions undergoing FFR evaluation (49). The aim was to test the hypothesis that PCI plus the best available medical therapy would be superior in reducing the rate of death, MI, or urgent coronary revascularization, compared with best available medical therapy alone. Patients who had no proven functionally significant lesion by FFR were enrolled into a registry and managed with optimal medical therapy. Although there were significant differences for the primary endpoint in favor of patients undergoing PCI (driven largely by reductions in the need for urgent coronary revascularization), patients enrolled into the registry had equivalent clinical outcomes to the PCI group. The angiographic findings of this group were not dissimilar to the randomized cohort, with 90% of patients having at least 1 epicardial stenosis of >50% diameter. The absence of a functionally significant epicardial lesion, despite the angiographic findings, portended a 3% occurrence of the primary endpoint, compared with 12.7% in the medically treated group ($p < 0.001$). A 4.3% rate of the primary endpoint in the PCI-treated group, compared evenly with those patients without a functionally significant epicardial lesion ($p = 0.61$). In addition, despite the trial being underpowered and stopped early, there was a trend toward a 39% relative risk reduction in death or AMI in the PCI-treated group compared with the medically treated group (hazard ratio [95% confidence interval]: 0.61 [0.28 to 1.35], $p = 0.22$). Acknowledging the various limitations of this trial, the FAME 2 result underscores the importance of the presence of functionally significant epicardial lesion as an adverse prognosticator in the short to medium term.

Further to this reasoning, Bangalore at al. (50) undertook a meta-analysis in an attempt to evaluate the association of PCI compared with optimal medical therapy, in stable patients with ischemic coronary artery disease, on the occurrence of various types of MI: either spontaneous nonprocedural MI, procedural-related MI, or "all MI," which included procedural MI. Although PCI for stable, obstructive lesions reduced the rate of spontaneous MI, this occurred at the expense of a higher risk of procedural-related MI. However, spontaneous MI carried a considerably higher risk of mortality than procedural-related MI, such that the point estimate for reduced mortality with PCI compared with medical therapy alone paralleled the prevention of spontaneous MI following PCI. These results provide a level of support to the findings of FAME 2 in that functionally significant lesions noted in angiography are commonly obstructive (>50% diameter stenosis, and thus amenable for revascularization), and are thus not "mild," and do not necessarily have a benign course despite the use of optimal

medical therapies. Although such lesions may not strictly conform to the consensus definition of a pathological vulnerable plaque, such lesions could be considered high risk from a clinical perspective.

Implications for Future Vulnerable Plaque Imaging Trials

Contemporary medical therapies, particularly dual antiplatelet and high-intensity statin therapies, have undoubtedly altered the natural history of coronary atherosclerosis, and curbed subsequent clinical event rates, even in patients considered at greatest risk for secondary coronary events. Indeed, MACE rates in the PROSPECT, PREDICTION (Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology), and FAME 2 trials were largely driven by the need for repeat coronary revascularization (36,43,49), considered by many to not represent a "hard" clinical event. However, it is important to note that percutaneous coronary revascularization per se, even for stable ischemic or functionally significant coronary lesions, should not necessarily be considered a benign undertaking, as there are inherent risks attributable to this procedure (50), and revascularization may indeed improve the morbidity and mortality of these patients (50–52). These observations have made the task for natural history studies of coronary atheroma rather difficult to draw strong associations between incident hard clinical events and underlying plaque morphology. Although ethically feasible to undertake intravascular imaging in patients undergoing a clinically indicated coronary angiogram, it is highly unethical to deny patients the best available medical therapy following acute coronary syndromes. This has important implications for the design of studies that attempt to link prospective hard clinical events with de novo coronary plaque phenotype.

In the current era, evidence and guidelines support lowering of low-density lipoprotein cholesterol levels to below 70 mg/dl in patients with coronary disease, resulting in coronary atheroma regression in a majority of individuals (39,40). As such, are hard clinical events still the most appropriate endpoints for imaging studies of coronary atherosclerosis? Rather, should primary endpoints of imaging trials focus on the surrogate marker of disease progression despite optimal medical therapies? One such proposition is to consider the "softer" findings of plaque/lesion progression and/or coronary revascularization as valid surrogate endpoints in clinical studies assessing potential vulnerable plaque phenotype in a secondary preventive setting. As witnessed in FAME 2, 50% of patients requiring urgent coronary revascularization presented with either a biomarker-positive acute coronary syndrome, or with ischemic electrocardiographic abnormalities (49). Although these are not desirable clinical endpoints in clinical outcomes trials, the alternative would be to undertake a clinical outcomes trial in huge numbers of patients with extended

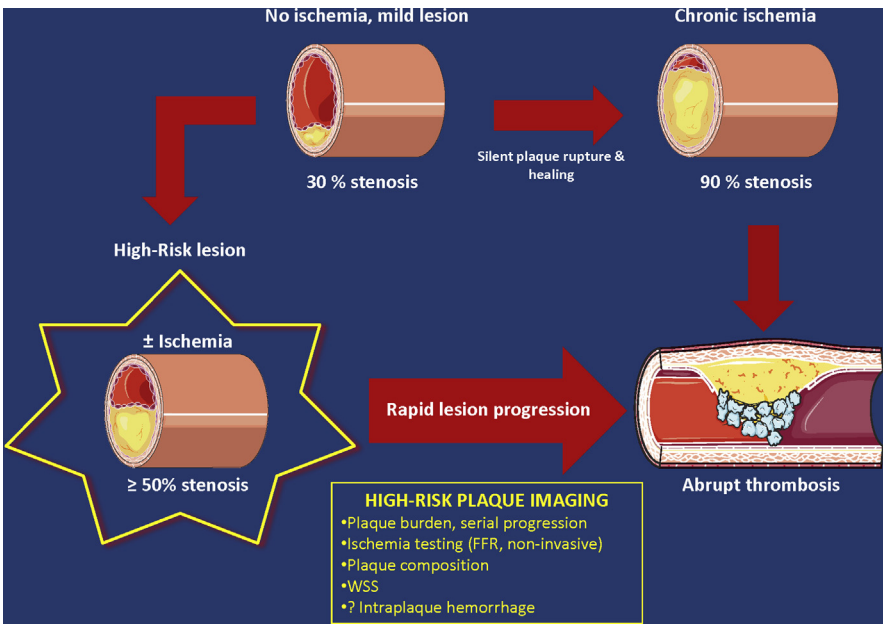

Figure 2 Proposed Pathway of Coronary Lesions Leading to AMI

There are a number of pathways that result in lesions causing acute myocardial infarction (AMI). On the basis of current clinical evidence, we propose that lesions with the greatest propensity for causing myocardial infarction are those that are at least 50% stenotic on a coronary angiogram, that undergo rapid lesion progression, and/or that are ischemic. FFR = fractional flow reserve; WSS = wall shear stress.

(>5 years) clinical follow-up in order to draw clinically meaningful associations between vulnerable plaque phenotype and hard coronary events. Indeed, the financial implications of conducting such a trial may prove prohibitive. It may thus be necessary to broaden the scope of coronary imaging studies to include the potential evaluation of asymptomatic patients considered intermediate-to-high cardiovascular risk for AMI, in order to capture more of the >1 million people annually that succumb to AMI or its complications in the United States alone. This would, however, require the use of noninvasive coronary imaging, which currently lacks the imaging resolution and technology to reliably image targets of plaque vulnerability within the coronary arterial wall. Furthermore, the lower clinical event rate observed in a more general population, coupled with the lower diagnostic accuracy of these noninvasive imaging tools, is likely to lead to a reduced sensitivity and specificity. This, however, may be overcome by enriching the studied population via known (or soon-to-be validated) plasma biomarkers that relate to future MACE. One such current example is the current controversial role of systemic inflammation (plasma C-reactive protein levels) in providing incremental risk-predictive capabilities beyond cholesterol levels (53). Thus, the interplay between high plaque burden and composition, lesion progression, lesion-related ischemia, and high C-reactive protein levels may more readily optimize the identification of vulnerable patients that harbor high-risk plaque more likely to associate with an incident clinical event. Efforts are already underway to utilize various noninvasive imaging and plasma biomarkers for prospective risk assessment in individuals without known atherothrombotic disease, yet considered at risk for short- to intermediate-term cardiovascular events (54).

Conclusions

Contemporary analyses demonstrate that many AMIs could arise from obstructive lesions (>50% angiographic stenosis severity), either close to or at the time of the event. Before causing an AMI, it is possible that these lesions harbored ischemic potential, possessing a critical, large burden of plaque that remained susceptible to repeated cycles of plaque rupture and intraplaque hemorrhage. This sets the substrate for further plaque progression, lumen encroachment and unstable symptoms, and/or uncontained in situ thrombosis and subsequent AMI (Fig. 2). In addition, we propose that lesions containing large plaque burden and/or ischemic potential within at-risk patients, should be the focus of imaging evaluation in the setting of appropriately designed clinical studies to identify processes that drive lesion progression and promote lesion instability.

Reprint requests and correspondence: Dr. Samir R. Kapadia, Department of Cardiovascular Medicine, Heart and Vascular Institute, Mail Code J2-3, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: kapadis@ccf.org.

REFERENCES

1. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733–43.
2. Schaar JA, Muller JE, Falk E, et al. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. Eur Heart J 2004;25:1077–82.
3. Zaman T, Agarwal S, Anabtawi AG, et al. Angiographic lesion severity and subsequent myocardial infarction. Am J Cardiol 2012;110:167–72.
4. Fearon WF. Is a myocardial infarction more likely to result from a mild coronary lesion or an ischemia-producing one? Circ Cardiovasc Interv 2011;4:539–41.
5. Burke AP, Kolodgie FD, Farb A, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 2001;103:934–40.
6. Schwartz RS, Burke A, Farb A, et al. Microemboli and microvascular obstruction in acute coronary thrombosis and sudden coronary death: relation to epicardial plaque histopathology. J Am Coll Cardiol 2009;54:2167–73.
7. Narula J, Nakano M, Virmani R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol 2013;61:1041–51.
8. Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. Heart 1999;82:265–8.
9. Nesto RW, Waxman S, Mittleman MA, et al. Angioscopy of culprit coronary lesions in unstable angina pectoris and correlation of clinical presentation with plaque morphology. Am J Cardiol 1998;81:225–8.
10. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. Br Heart J 1983;50:127–34.
11. Bruschke AV, Kramer JR Jr., Bal ET, Haque IU, Detrano RC, Goormastic M. The dynamics of progression of coronary atherosclerosis studied in 168 medically treated patients who underwent coronary arteriography three times. Am Heart J 1989;117:296–305.
12. Lichtlen PR, Nikutta P, Jost S, Deckers J, Wiese B, Rafflenbeul W, The INTACT Study Group. Anatomical progression of coronary artery disease in humans as seen by prospective, repeated, quantitated coronary angiography. Relation to clinical events and risk factors. Circulation 1992;86:828–38.
13. Moise A, Theroux P, Taeymans Y, et al. Clinical and angiographic factors associated with progression of coronary artery disease. J Am Coll Cardiol 1984;3:659–67.
14. Yokoya K, Takatsu H, Suzuki T, et al. Process of progression of coronary artery lesions from mild or moderate stenosis to moderate or severe stenosis: a study based on four serial coronary arteriograms per year. Circulation 1999;100:903–9.
15. Kolodgie FD, Gold HK, Burke AP, et al. Intraplaque hemorrhage and progression of coronary atheroma. N Engl J Med 2003;349:2316–25.
16. Finn AV, Narula J. Intraplaque hemorrhage: most dangerous is the wound that bleedeth inwardly. J Am Coll Cardiol Img 2012;5:856–8.
17. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56–62.
18. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988;78:1157–66.
19. Giroud D, Li JM, Urban P, Meier B, Rutishauer W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. Am J Cardiol 1992;69:729–32.
20. Dacanay S, Kennedy HL, Uretz E, Parrillo JE, Klein LW. Morphological and quantitative angiographic analyses of progression of coronary stenoses. A comparison of Q-wave and non-Q-wave myocardial infarction. Circulation 1994;90:1739–46.
21. Hackett D, Verwilghen J, Davies G, Maseri A. Coronary stenoses before and after acute myocardial infarction. Am J Cardiol 1989;63:1517–8.
22. Ojio S, Takatsu H, Tanaka T, et al. Considerable time from the onset of plaque rupture and/or thrombi until the onset of acute myocardial infarction in humans: coronary angiographic findings within 1 week before the onset of infarction. Circulation 2000;102:2063–9.
23. Frobert O, van't Veer M, Aarnoudse W, Simonsen U, Koolen JJ, Pijls NH. Acute myocardial infarction and underlying stenosis severity. Catheter Cardiovasc Interv 2007;70:958–65.

24. Brown BG, Gallery CA, Badger RS, et al. Incomplete lysis of thrombus in the moderate underlying atherosclerotic lesion during intracoronary infusion of streptokinase for acute myocardial infarction: quantitative angiographic observations. Circulation 1986;73:653–61.
25. Manoharan G, Ntalianis A, Muller O, et al. Severity of coronary arterial stenoses responsible for acute coronary syndromes. Am J Cardiol 2009;103:1183–8.
26. Schmidt WG, Uebis R, von Essen R, et al. Residual coronary stenosis after thrombolysis with rt-PA or streptokinase: acute results and 3 weeks follow-up. Eur Heart J 1987;8:1182–8.
27. Ellis S, Alderman EL, Cain K, Wright A, Bourassa M, Fisher L. Morphology of left anterior descending coronary territory lesions as a predictor of anterior myocardial infarction: a CASS Registry study. J Am Coll Cardiol 1989;13:1481–91.
28. Alderman EL, Corley SD, Fisher LD, et al., CASS Participating Investigators and Staff. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). J Am Coll Cardiol 1993;22:1141–54.
29. Mancini GB, Hartigan PM, Bates ER, et al. Angiographic disease progression and residual risk of cardiovascular events while on optimal medical therapy: observations from the COURAGE trial. Circ Cardiovasc Interv 2011;4:545–52.
30. Ringqvist I, Fisher LD, Mock M, et al. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). J Clin Invest 1983;71:1854–66.
31. Mintz GS, Painter JA, Pichard AD, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. J Am Coll Cardiol 1995;25:1479–85.
32. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5.
33. Schoenhagen P, Ziada KM, Vince DG, Nissen SE, Tuzcu EM. Arterial remodeling and coronary artery disease: the concept of "dilated" versus "obstructive" coronary atherosclerosis. J Am Coll Cardiol 2001;38:297–306.
34. Nicholls SJ, Hsu A, Wolski K, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol 2010;55:2399–407.
35. Puri R, Wolski K, Uno K, et al. Left main coronary atherosclerosis progression, constrictive remodeling, and clinical events. J Am Coll Cardiol Intv 2013;6:29–35.
36. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.
37. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) study. J Am Coll Cardiol Img 2011;4:894–901.
38. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295:1556–65.
39. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011;365:2078–87.
40. Puri R, Nissen SE, Ballantyne CM, et al. Factors underlying regression of coronary atheroma with potent statin therapy. Eur Heart J 2013;34:1818–25.
41. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 2003;290:2292–300.
42. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA 2007;297:499–508.
43. Stone PH, Saito S, Takahashi S, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION study. Circulation 2012;126:172–81.
44. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. J Am Coll Cardiol 2007;49:2105–11.
45. Pavin D, Delonca J, Siegenthaler M, Doat M, Rutishauser W, Righetti A. Long-term (10 years) prognostic value of a normal thallium-201 myocardial exercise scintigraphy in patients with coronary artery disease documented by angiography. Eur Heart J 1997;18:69–77.
46. Vanzetto G, Ormezzano O, Fagret D, Comet M, Denis B, Machecourt J. Long-term additive prognostic value of thallium-201 myocardial perfusion imaging over clinical and exercise stress test in low to intermediate risk patients: study in 1137 patients with 6-year follow-up. Circulation 1999;100:1521–7.
47. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.
48. Farzaneh-Far A, Phillips HR, Shaw LK, et al. Ischemia change in stable coronary artery disease is an independent predictor of death and myocardial infarction. J Am Coll Cardiol Img 2012;5:715–24.
49. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.
50. Bangalore S, Pursnani S, Kumar S, Bagos PG. Percutaneous coronary intervention versus optimal medical therapy for prevention of spontaneous myocardial infarction in subjects with stable ischemic heart disease. Circulation 2013;127:769–81.
51. Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet 2006;368:998–1004.
52. Hannan EL, Samadashvili Z, Cozzens K, et al. Comparative outcomes for patients who do and do not undergo percutaneous coronary intervention for stable coronary artery disease in New York. Circulation 2012;125:1870–9.
53. Ridker PM, Kastelein JJ, Genest J, Koenig W. C-reactive protein and cholesterol are equally strong predictors of cardiovascular risk and both are important for quality clinical care. Eur Heart J 2013;34:1258–61.
54. Muntendam P, McCall C, Sanz J, Falk E, Fuster V. The BioImage study: novel approaches to risk assessment in the primary prevention of atherosclerotic cardiovascular disease—study design and objectives. Am Heart J 2010;160:49–57.e1.

Key Words: atherosclerosis ■ myocardial infarction ■ myocardial ischemia ■ plaque.