

# Do Plaques Rapidly Progress Prior to Myocardial Infarction?

## The Interplay Between Plaque Vulnerability and Progression

Amir Ahmadi, Jonathon Leipsic, Ron Blankstein, Carolyn Taylor, Harvey Hecht, Gregg W. Stone, Jagat Narula

**Abstract:** There is a common misperception in the cardiology community that most acute coronary events arise from ruptures of mildly stenotic plaques. This notion has emanated from multiple studies that had measured the degree of angiographic luminal narrowing in culprit plaques months to years before myocardial infarction. However, angiographic studies within 3 months before myocardial infarction, immediately after myocardial infarction with thrombus aspiration or fibrinolytic therapy, and postmortem pathological observations have all shown that culprit plaques in acute myocardial infarction are severely stenotic. Serial angiographic studies also have demonstrated a sudden rapid lesion progression before most cases of acute coronary syndromes. The possible mechanisms for such rapid plaque progression and consequent luminal obstruction include recurrent plaque rupture and healing and intraplaque neovascularization and hemorrhage with deposition of erythrocyte-derived free cholesterol. Moreover, recent intravascular and noninvasive imaging studies have demonstrated that plaques which result in coronary events have larger plaque volume and necrotic core size with greater positive vessel remodeling compared with plaques, which remain asymptomatic during several years follow-up, although these large atheromatous vulnerable plaques may angiographically seem mild. As such, it is these vulnerable plaques which are more prone to rapid plaque progression or are those in which plaque progression is more likely to become clinically evident. Therefore, in addition to characterizing plaque morphology, inflammatory activity, and severity, detection of the rate of plaque progression might identify vulnerable plaques with an increased potential for adverse outcomes. (*Circ Res.* 2015;117:99-104. DOI: 10.1161/CIRCRESAHA.117.305637.)

**Key Words:** acute coronary syndrome ■ atherosclerosis ■ coronary artery disease ■ myocardial infarction

Pathological and anatomic features of high-risk or vulnerable plaques have been reviewed extensively in the literature.<sup>1</sup> Briefly, high-risk plaques are characterized by the presence of large plaque burden and necrotic cores that are covered by intensely inflamed, thin fibrous caps; these lesions are typically positively (or outwardly) remodeled.<sup>1</sup> Most of the anatomic features of high-risk plaques are identifiable in vivo using invasive and noninvasive imaging modalities, such as intravascular ultrasound, optical coherence tomography, and coronary computed tomography angiography. Although difficult, inflammation has been identified by intravascular demonstration of thermal heterogeneity and targeting of macrophages by positron emission tomography.<sup>2-13</sup> Studies over the past 2 decades have demonstrated that high-risk plaques are usually responsible for most acute coronary syndromes (ACS).<sup>1,14-17</sup> However, despite extensive interest and excitement regarding the potential of identifying high-risk lesions,

plaque characteristics that have been shown to be associated with high-risk plaques have demonstrated a poor positive predictive value for identifying future events.<sup>18</sup>

For more than a decade, the cardiology community has believed that most ACS arise from ruptures of mildly stenotic plaques and that most major adverse events occur independent of the plaque size and the degree of luminal stenosis.<sup>19</sup> This belief emanated from retrospective studies of patients in whom coronary angiography had been performed months to years before myocardial infarction (MI); the lesions responsible for the subsequent infarct were angiographically mild in most cases, that is, at baseline <50% diameter stenosis compared with the adjacent reference vessel lumen.<sup>20-24</sup> Pathologically, although some coronary events may be caused by rupture of plaques with a mild degree of luminal narrowing,<sup>17</sup> most culprit lesions at the time of the acute event are critically occlusive.<sup>15,17,25-30</sup> A postmortem study of patients

Original received November 13, 2014; revision received May 1, 2015; accepted May 5, 2015. In April 2015, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 13.84 days

From the Division of Cardiology, Icahn School of Medicine at Mount Sinai, New York, NY (A.A., H.H., J.N.); Division of Cardiology (A.A., J.L., C.T.), and Division of Radiology (J.L.), University of British Columbia, Vancouver, BC, Canada; Division of Cardiovascular Medicine, Brigham and Women Hospital, Harvard Medical School, Boston, MA (R.B.); and Medical Center and the Cardiovascular Research Foundation, Columbia University, New York, NY (G.W.S.).

Correspondence to Jagat Narula, MD, PhD, Professor Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029. E-mail jagat.narula@mountsinai.org

© 2015 American Heart Association, Inc.

*Circulation Research* is available at <http://circres.ahajournals.org>

DOI: 10.1161/CIRCRESAHA.117.305637

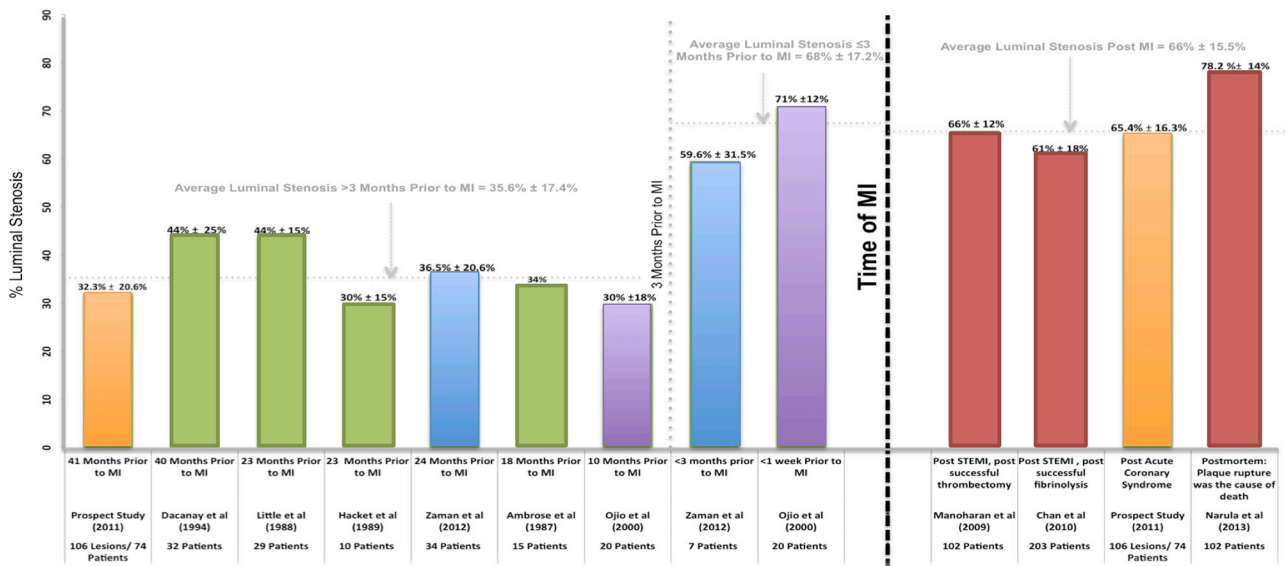
Nonstandard Abbreviations and Acronyms	
ACS	acute coronary syndromes
MI	myocardial infarction
STEMI	ST-segment elevation MI

who died suddenly<sup>17</sup> demonstrated that >70% of ruptured plaques exhibited >75% (mean 78%±14%) cross-sectional area narrowing; only ≈5% of the fatal events were caused by the lesions <50% cross-sectional luminal narrowing.<sup>17</sup> Studies in patients at the time of MI are consistent with these findings. Following successful fibrinolysis in patients with acute ST-segment elevation MI (STEMI), the average luminal stenosis caused by culprit lesions (excluding those with obvious residual thrombus) as assessed by quantitative coronary angiography was reported to be 61%±17%.<sup>25</sup> Similarly, the average stenosis of the infarct related lesion in STEMI patients who underwent thrombus aspiration was reported as 66%±12%<sup>26</sup> (Figure 1). Although other post MI studies in the absence of thrombolytic therapy or thrombus aspiration have also

confirmed a significant degree of stenosis of the infarct-related artery, some overestimation of the luminal stenosis caused by residual thrombus cannot be ruled out.<sup>27–29</sup>

A critical review of the literature suggests that the apparent discordance regarding the severity of culprit lesions may be explained by understanding the time course of the development and maturation of atherosclerotic plaques (Figure 1). The common feature in all of the original studies that linked mild plaques to MI is the long lead time between the baseline angiogram and the acute event (average, 25 months, range 18–40 months) (Figure 1).<sup>20–24</sup> More recent studies have demonstrated that plaques progress from mild at baseline to obstructive at the time of MI and clarified that plaque progression occurs before actual plaque rupture.<sup>16,31–33</sup> In addition, as described later, angiography often substantially underestimates plaque severity, as revealed by intravascular ultrasound imaging, contributing to the misconception of the mild vulnerable plaque.

The Providing Regional Observations to Study Predictors of Events in the Coronary Tree study<sup>16</sup> (PROSPECT) prospectively found that among 106 nonculprit lesions in 697 patients resulting in subsequent ACS during median 3.4 year

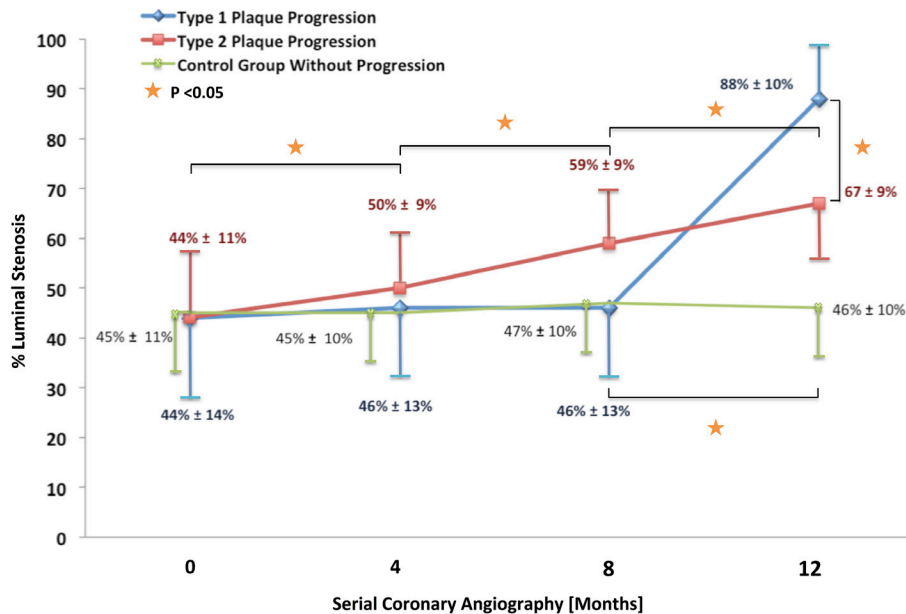


**Figure 1. Do plaques rapidly progress before myocardial infarction?** This figure illustrates average luminal stenosis of culprit lesions resulted in MI\* in various studies, organized relative to the time of MI. Green bars represent average luminal stenosis of the culprit lesions before MI, whereas red bars signify organized measurement after MI. Both green and red bars represent studies with single measurement. Data from studies with >1 measurement are shown by paired colors (orange, blue, and purple). The common perception that most MI are caused by rupture of mild plaques emerged from studies in 1980s and 1990s (2nd, 3rd, 4th, 6th bar from left)<sup>16,17,19,20</sup> which reported that lesions responsible for the subsequent STEMI were angiographically mild at baseline. In studies in which measurements were made >3 months before MI, the mean luminal stenosis by culprit lesion was 35.6%±20.6%. On average, these measurements were done 25 months before MI (range 18–41 months). On the other hand, data emerging from studies that investigated culprit lesion after the MI shows obstructive lesions are responsible for MI with mean luminal stenosis of 66%±15.5% (red bars). (We only included post-STEMI data with successful fibrinolysis or thrombectomy along with postmortem data in this figure to ensure measurements were not significantly affected by the presence of thrombus and accurately reflect plaque size.) The PROSPECT study<sup>11</sup> along with studies by Zaman<sup>28</sup> and Ojio<sup>29</sup> shed light on this apparent discrepancy in the literature. PROSPECT (orange bars)<sup>11</sup> demonstrated progression of lesion from 32.3%±20.6% at baseline to 65.4%±16.3% at the time of event (during a median follow-up of 3.4 years). In a study by Zaman et al (blue bars),<sup>28</sup> among 41 patients who had STEMI, culprit lesions that were measured >3 months (mean 24 months) before MI had mean luminal stenosis of 36.5%±20.6%, whereas culprit lesions that were measured <3 months before MI had mean luminal stenosis of 59.6%±31.5%. Similarly, in a study by Ojio et al (purple bars),<sup>29</sup> the mean luminal stenosis of culprit lesions 10 months before MI was 30%±18%, whereas similar measurement less than a week before MI revealed culprit lesions causing luminal stenosis of 71%±12%. Overall, the totality of the data represented in this figure demonstrates that culprit lesions go through a period of rapid progression weeks to months before MI. This observation can explain the apparent discrepancy in the literature between size of culprit plaques at baseline and at the time of event. The culprit lesions in PROSPECT study (orange bar) and study by Ojio et al (purple bar) resulted in variety of acute coronary syndromes (ACS) presentations, whereas the culprit lesions in the rest of studies represented here resulted in STEMI. MI indicates myocardial infarction; and STEMI, ST elevation myocardial infarction.

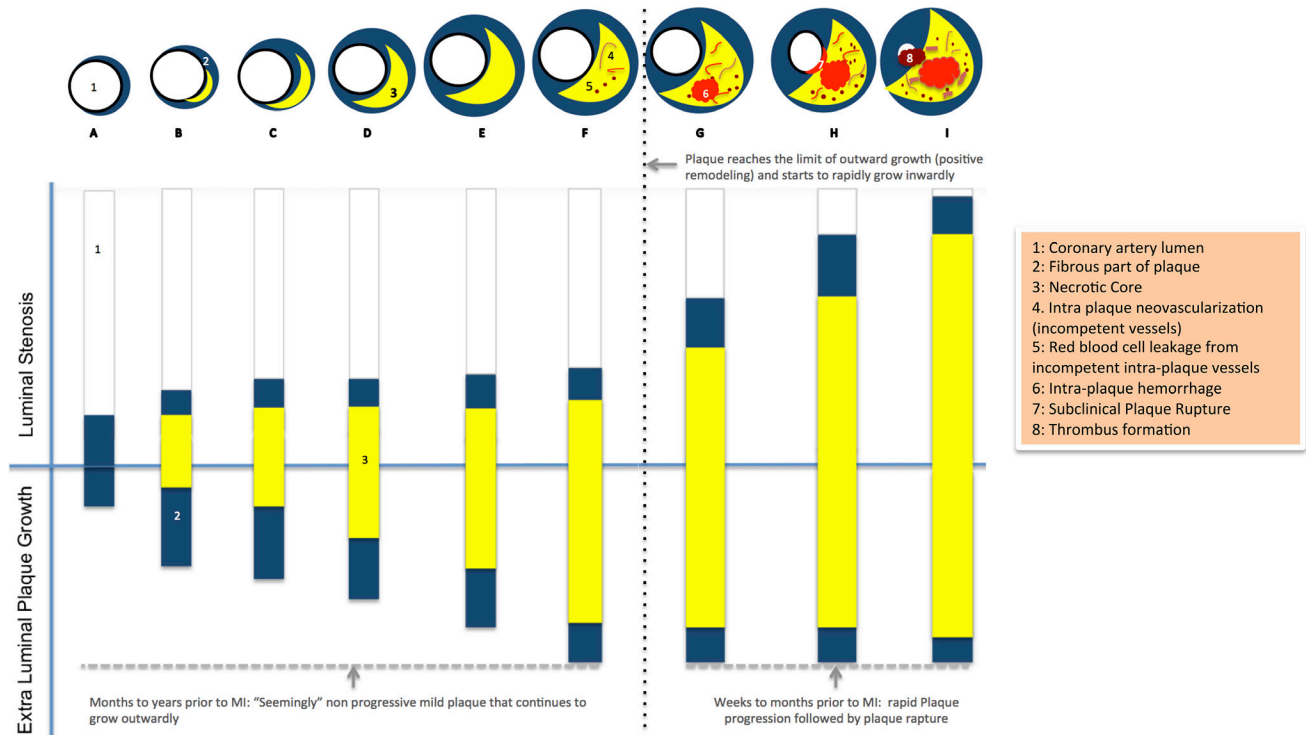
follow-up, there was progression from a mean angiographic diameter stenosis of  $32\% \pm 21\%$  at baseline to  $65\% \pm 16\%$  at the time of occurrence of the acute event. In the Dynamic Registry of the National Heart, Lung, and Blood Institute,<sup>31</sup> 3747 patients undergoing percutaneous coronary intervention were retrospectively studied. In this cohort, 216 patients required an additional percutaneous coronary intervention of a nonculprit lesion within 1 year. The mean diameter stenosis of the (originally) nonculprit lesion progressed from a baseline value of  $41.8\% \pm 20.8\%$  to  $83.9\% \pm 13.9\%$  at the time of the subsequent percutaneous coronary intervention. Thus, these studies clearly demonstrate plaque progression from the time of initial angiography to the acute event. Another set of studies<sup>32,33</sup> in STEMI patients wherein previous angiographic data were available has further clarified the dynamics and rate of plaque progression before MI. The average diameter stenosis of lesions that eventually led to STEMI (28) and were identified on angiography >3 months before the acute event was  $36.5\% \pm 20.6\%$  by quantitative coronary angiography. Conversely, the average diameter stenosis of the lesions that resulted in STEMI within the next 3 months was  $59.1\% \pm 31.5\%$ <sup>32</sup> (Figure 1). A similar study segregated patients who had undergone coronary angiography either within days before their MI or more remotely.<sup>33</sup> If the elective diagnostic coronary angiography was performed within 1 week

before MI (mean,  $3 \pm 3$  days), the mean diameter stenosis of the fateful lesions was  $71\% \pm 12\%$  compared with  $30\% \pm 18\%$  in patients who underwent coronary angiography 6 to 18 months before MI (mean,  $282 \pm 49$  days; Figure 1). It is thus reasonable to hypothesize that lesions leading to MI enlarge in the months to weeks before MI, helping to explain why plaques causing MI are mild many months before the acute event but obstructive at the time of the event.

The understanding of the complex dynamics of plaque progression before MI is of paramount importance. Most studies of plaque progression with serial coronary angiography have found the process to be nonlinear and variable with an unpredictable course.<sup>34-36</sup> A unique Japanese study has illustrated this hypothesis in a serial angiographic evaluation. Yokoya and colleagues performed 4 coronary angiograms within a 1-year period, at 4 month intervals (ie, at mean time 0, 4, 8, and 12 months).<sup>37</sup> They observed 3 different types of plaque progression (Figure 2). Type I plaques ( $n=14$ ; Figure 2, blue line) did not have significant progression in the initial 3 angiograms followed by a very rapid and sudden progression between the third and fourth angiogram; 70% of these patients developed unstable angina or acute MI. Type II plaques ( $n=22$ ; Figure 2, red line) showed a steady and slow progression over the entire 1-year length of the study, and no MI was reported in this group; 14% of these patients, however,



**Figure 2. Not all plaques progress the same way.** This figure, modified from the study by Yokoya et al.<sup>37</sup> illustrates different types of plaque progression. In this study, 36 objective vessels (36 patients) with clinically significant coronary stenosis progression at 1 year ( $\geq 15\%$  increase in luminal narrowing from a mild plaque with baseline diameter stenosis  $>20\%$ ) in whom 4 coronary angiograms were performed at 4-month intervals were investigated. They were compared with a control group of 50 patients who did not have a significant coronary stenosis progression in the similar time period. Two distinct type of plaque progression were noted. In type 1 plaque progression ( $n=14$ ), the mean diameter stenosis did not change in the first 3 measurements, but a sudden marked increase was observed between the 3rd and 4th measurements. Seventy-one percent of lesions with this type of plaque progression resulted in unstable angina or an MI. In type 2 plaque progression ( $n=22$ ), the mean diameter stenosis increased constantly in all intervals from the first to final coronary angiogram. In this group, there were no MIs, although 14% of patients experienced angina pectoris when the diameter stenosis reached a severe level. There was no significant progression in the control group, and only 1 patient (2%) developed new onset angina. An interesting observation is that in the setting of type 1 plaque progression, if the information from the second to fourth angiogram was not available, one could have mistakenly concluded that plaques with 44% diameter stenosis on average (at the time of first angiogram) resulted in acute events during follow-up. However, we can clearly observe through serial angiography that these plaques have undergone rapid and sudden progression before causing MI. Adapted from Yokoya et al<sup>37</sup> with permission of the publisher. Copyright ©1999, Wolters Kluwer Health. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.



**Figure 3. Possible mechanism for rapid plaque progression before MI.** This figure illustrates a biologically plausible mechanism for rapid plaque progression before MI. The plaque depicted here is going through outward expansion (positive remodeling) in the first 6 measurements (A–F). During this time, the degree of luminal narrowing is relatively stable, despite active plaque growth, emphasizing that a stable degree of luminal narrowing is not equivalent to lack of plaque growth. Between stages F and G, the plaque reaches the limit of outward expansion (dotted line) and intraluminal growth ensues causing accelerated luminal narrowing. The possible mechanisms for this rapid expansion include intraplaque neovascularization with incompetent vessels that leak red blood cells at the borders of the necrotic core (F–H), intraplaque hemorrhage (G–I), and subclinical cycles of rupture and healing (H) causing accelerated plaque growth. Finally, a rapidly grown plaque ruptures and causes intraluminal thrombus formation resulting in a myocardial infarction (I). It should be noted that histological and behavioral features that allow plaques to undergo such rapid progression are the same features that are known to be characteristics of vulnerable plaques. It is also known that most MIs are result of ruptures of plaques with these features. Therefore, in order for a plaque to grow rapidly before causing MI, it should already possess or acquire these features of vulnerability. MI indicates myocardial infarction.

developed angina pectoris when the diameter stenosis became severe (Figure 2). There were no significant differences in the use of medications, smoking status, obesity, or family history of premature coronary disease between the 2 groups.<sup>37</sup> The third type of plaque (control lesions, n=50) did not change from the baseline during the year (Figure 2, green line); new onset angina developed in only 1 of these patients (2%), and none developed MI. This study demonstrates that there are different patterns of plaque progression and, in concert with the prior studies (Figure 1), suggests that sudden, rapid plaque progression precedes MI in the majority of cases.

The pioneering work of Glagov and colleagues<sup>39</sup> using invasive and noninvasive imaging<sup>2,38</sup> confirmed that the growth of the lipid-rich atherosclerotic plaques initially manifests with outward plaque expansion (ie, positive vessel remodeling) to preserve luminal dimensions and coronary flow reserve. It seems that further outward expansion is limited when the plaque occupies  $\approx 40\%$  of the cross-sectional luminal area, after which further plaque progression necessarily encroaches on the lumen.<sup>39</sup> It should be noted that during the time of outward expansion, if plaque progression is assessed solely by luminal narrowing measurements (eg, coronary angiography), a plaque that is actively expanding outwardly might be mistakenly considered a stable, nonprogressive and mild

plaque (Figure 3). The misconception of the angiographically mild vulnerable plaque was first prospectively exposed in the PROSPECT study. By radiofrequency intravascular ultrasound imaging, plaques that were responsible for ACS during 3-year follow-up were more likely at baseline to have large plaque burden and a small minimal lumen area (in addition to being classified as a thin-cap fibroatheroma), despite appearing angiographically mild.<sup>13</sup>

The exact mechanism of rapid plaque progression is not yet fully understood. It is known that mildly obstructive plaques with vulnerable features can rupture and heal subclinically, and these cycles of rupture and healing can lead to progressive plaque expansion until symptoms and vessel occlusion occur.<sup>30,40</sup> In addition, neovascularization at the borders of necrotic core commonly accompanies plaque growth with mural hypoxia. These nascent vessels are not enveloped by smooth muscle cells and leak macromolecules into the plaque microenvironment, including erythrocytes. The red blood cells are rich in free cholesterol and contribute to the expansion of the necrotic core region<sup>41</sup> (Figure 3). These neovasculature are fragile and may result in intraplaque hemorrhage with plaque expansion.<sup>42,43</sup> Increasing inflammation within the plaque with consequent increase in cytokines and matrix alterations can not only contribute directly to the plaque expansion but may

also lead to progressive fibrous cap thinning and likelihood of subclinical or overt plaque rupture.<sup>44,45</sup>

Although it is well established that plaques with vulnerable features are responsible for most MI, not all plaques with such features lead to an acute event. In a postmortem study,<sup>17</sup> one of the major differences between the ruptured plaques and high-risk plaques with similar histological features was significantly larger size of ruptured plaques. In a prospective coronary computed tomographic angiography,<sup>14</sup> only 22% of patients with plaques with 2 vulnerable features (positive remodeling and large necrotic cores) developed acute events. These plaques had a significantly larger remodeling index ( $126.7 \pm 3.9$  versus  $113.4 \pm 1.6$ ), total plaque volume ( $134.9 \pm 14.1$  mm<sup>3</sup> versus  $57.8 \pm 5.7$  mm<sup>3</sup>), and necrotic core volume ( $20.4 \pm 3.4$  mm<sup>3</sup> versus  $1.1 \pm 1.4$  mm<sup>3</sup>) compared with uneventful plaques with high-risk features. Another serial computed tomography angiography study demonstrated that the high-risk plaques only resulted in an acute event if they were associated with plaque progression<sup>46</sup> suggest that among plaques with features of vulnerability, those with a higher degree of progression have much greater likelihood to result in ACS.

### Conclusions

Although a small proportion of truly mild plaques might rupture and become symptomatic, most plaques that are destined to cause events typically undergo rapid plaque progression in the weeks to months before MI and have large atheroma volume with large necrotic cores at the time of event. Asymptomatic lesion progression of milder plaques might result from subclinical cycles of rupture and healing and intraplaque neovascularization and hemorrhage. Given that only a minority of plaques with vulnerable features will result in coronary events and that such plaques have larger volume and necrotic core size with greater expansive remodeling compared with those which do not become symptomatic in the intermediate term, we propose that rapid plaque progression of moderately severe vulnerable plaques is the critical step before MI in most cases. It is conceivable that in addition to characterizing plaque morphology and inflammatory activity, detection of the rate of plaque progression might identify vulnerable plaques with an increased potential for adverse outcomes. With rapid plaque progression having been demonstrated as a prerequisite to MI in most patients, we further think that it is time to shift perspective from plaque size as a static concept to more of a dynamic one, as the rate of progression might prove to be as or more important than the absolute degree of plaque burden and luminal narrowing. As the data available to support this perspective emerge from small studies, larger studies to further investigate these concepts are warranted.

### Disclosures

None.

### References

- Kolodgie FD, Virmani R, Burke AP, Farb A, Weber DK, Kutys R, Finn AV, Gold HK. Pathologic assessment of the vulnerable human coronary plaque. *Heart*. 2004;90:1385–1391. doi: 10.1136/hrt.2004.041798.
- Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:319–326. doi: 10.1016/j.jacc.2007.03.044.
- Maurovich-Horvat P, Hoffmann U, Vorpahl M, Nakano M, Virmani R, Alkadhi H. The napkin-ring sign: CT signature of high-risk coronary plaques? *JACC Cardiovasc Imaging*. 2010;3:440–444. doi: 10.1016/j.jcmg.2010.02.003.
- Nishio M, Ueda Y, Matsuo K, Asai M, Nemoto T, Hirata A, Kashiwase K, Kodama K. Detection of disrupted plaques by coronary CT: comparison with angiography. *Heart*. 2011;97:1397–1402. doi: 10.1136/hrt.2011.227181.
- Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, Shimada K, Yoshiyama M. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc Imaging*. 2013;6:448–457. doi: 10.1016/j.jcmg.2012.09.016.
- Rogers IS, Tawakol A. Imaging of coronary inflammation with FDG-PET: feasibility and clinical hurdles. *Curr Cardiol Rep*. 2011;13:138–144. doi: 10.1007/s11886-011-0168-3.
- Rosa GM, Bauckneht M, Masoero G, Mach F, Quercioli A, Seitun S, Balbi M, Brunelli C, Parodi A, Nencioni A, Vuilleumier N, Montecucco F. The vulnerable coronary plaque: update on imaging technologies. *Thromb Haemost*. 2013;110:706–722. doi: 10.1160/TH13-02-0121.
- Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, Ozaki Y, Pinto F, Serruys PW; Expert's OCT Review Document. Expert review on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J*. 2010;31:401–415. doi: 10.1093/eurheartj/ehp433.
- Tearney GJ, Yabushita H, Houser SL, Aretz HT, Jang IK, Schlerendorf KH, Kauffman CR, Shishkov M, Halpern EF, Bouma BE. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation*. 2003;107:113–119.
- Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlerendorf KH, Kauffman CR, Shishkov M, Kang DH, Halpern EF, Tearney GJ. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002;106:1640–1645.
- Casscells W, Hathorn B, David M, Krabach T, Vaughn WK, McAllister HA, Bearman G, Willerson JT. Thermal detection of cellular infiltrates in living atherosclerotic plaques: possible implications for plaque rupture and thrombosis. *Lancet*. 1996;347:1447–1451.
- Naghavi M, Madjid M, Gul K, Siadaty MS, Litovsky S, Willerson JT, Casscells SW. Thermography basket catheter: in vivo measurement of the temperature of atherosclerotic plaques for detection of vulnerable plaques. *Catheter Cardiovasc Interv*. 2003;59:52–59. doi: 10.1002/ccd.10486.
- Stefanadis C, Diamantopoulos L, Vlachopoulos C, Tsiamis E, Dornellis J, Toutouzas K, Stefanadi E, Toutouzas P. Thermal heterogeneity within human atherosclerotic coronary arteries detected in vivo: A new method of detection by application of a special thermography catheter. *Circulation*. 1999;99:1965–1971.
- Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009;54:49–57. doi: 10.1016/j.jacc.2009.02.068.
- Calvert PA, Obaid DR, O'Sullivan M, Shapiro LM, McNab D, Densem CG, Schofield PM, Braganza D, Clarke SC, Ray KK, West NE, Bennett MR. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. *JACC Cardiovasc Imaging*. 2011;4:894–901. doi: 10.1016/j.jcmg.2011.05.005.
- Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235. doi: 10.1056/NEJMoa1002358.
- Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, Malik S, Fuster V, Finn AV. 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;61:1041–1051. doi: 10.1016/j.jacc.2012.10.054.
- Kaul S, Narula J. In search of the vulnerable plaque: is there any light at the end of the catheter? *J Am Coll Cardiol*. 2014;64:2519–2524. doi: 10.1016/j.jacc.2014.10.017.

19. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation*. 1995;92:657–671.
20. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation*. 1988;78:1157–1166.
21. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjelmahl-Monsen CE, Leavy J, Weiss M, Borrico S, Gorlin R, Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol*. 1988;12:56–62.
22. 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;69:729–732.
23. Hackett D, Verwilghen J, Davies G, Maseri A. Coronary stenoses before and after acute myocardial infarction. *Am J Cardiol*. 1989;63:1517–1518.
24. 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;90:1739–1746.
25. Chan KH, Chavantapipat C, Gattorna T, Chantadansuwan T, Kirby A, Madden A, Keech A, Ng MK. The relationship between coronary stenosis severity and compression type coronary artery movement in acute myocardial infarction. *Am Heart J*. 2010;159:584–592. doi: 10.1016/j.ahj.2009.12.036.
26. Manoharan G, Ntalianis A, Muller O, Hamilos M, Sarno G, Melikian N, Vanderheyden M, Heyndrickx GR, Wyffels E, Wijns W, De Bruyne B. Severity of coronary arterial stenoses responsible for acute coronary syndromes. *Am J Cardiol*. 2009;103:1183–1188. doi: 10.1016/j.amjcard.2008.12.047.
27. Frøbert O, van't Veer M, Aarnoudse W, Simonsen U, Koolen JJ, Pijls NH. Acute myocardial infarction and underlying stenosis severity. *Catheter Cardiovasc Interv*. 2007;70:958–965. doi: 10.1002/ccd.21280.
28. Van Lierde J, De Geest H, Verstraete M, Van de Werf F. Angiographic assessment of the infarct-related residual coronary stenosis after spontaneous or therapeutic thrombolysis. *J Am Coll Cardiol*. 1990;16:1545–1549.
29. Brown BG, Gallery CA, Badger RS, Kennedy JW, Mathey D, Bolson EL, Dodge HT. Incomplete lysis of thrombus in the moderate underlying atherosclerotic lesion during intracoronary infusion of streptokinase for acute myocardial infarction: quantitative angiographic observations. *Circulation*. 1986;73:653–661.
30. Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *N Engl J Med*. 1984;310:1137–1140. doi: 10.1056/NEJM198405033101801.
31. Glaser R, Selzer F, Faxon DP, Laskey WK, Cohen HA, Slater J, Detre KM, Wilensky RL. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. *Circulation*. 2005;111:143–149. doi: 10.1161/01.CIR.0000150335.01285.12.
32. Zaman T, Agarwal S, Anabtawi AG, Patel NS, Ellis SG, Tuzcu EM, Kapadia SR. Angiographic lesion severity and subsequent myocardial infarction. *Am J Cardiol*. 2012;110:167–172. doi: 10.1016/j.amjcard.2012.03.008.
33. 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;102:2063–2069.
34. Brusckhe 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.
35. Moise A, Thérout P, Taeymans Y, Waters DD, Lespérance J, Fines P, Descoings B, Robert P. Clinical and angiographic factors associated with progression of coronary artery disease. *J Am Coll Cardiol*. 1984;3:659–667.
36. Lichtlen PR, Nikutta P, Jost S, Deckers J, Wiese B, Rafflenbeul W. Anatomical progression of coronary artery disease in humans as seen by prospective, repeated, quantitated coronary angiography. Relation to clinical events and risk factors. The INTACT Study Group. *Circulation*. 1992;86:828–838.
37. Yokoya K, Takatsu H, Suzuki T, Hosokawa H, Ojio S, Matsubara T, Tanaka T, Watanabe S, Morita N, Nishigaki K, Takemura G, Noda T, Minatoguchi S, Fujiwara H. 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;100:903–909.
38. 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.
39. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Koletis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316:1371–1375. doi: 10.1056/NEJM198705283162204.
40. Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, Virmani R. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation*. 2001;103:934–940.
41. Kolodgie FD, Gold HK, Burke AP, Fowler DR, Kruth HS, Weber DK, Farb A, Guerrero LJ, Hayase M, Kutys R, Narula J, Finn AV, Virmani R. Intraplaque hemorrhage and progression of coronary atheroma. *N Engl J Med*. 2003;349:2316–2325. doi: 10.1056/NEJMoa035655.
42. Takaya N, Yuan C, Chu B, Saam T, Polissar NL, Jarvik GP, Isaac C, McDonough J, Natiello C, Small R, Ferguson MS, Hatsukami TS. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. *Circulation*. 2005;111:2768–2775. doi: 10.1161/CIRCULATIONAHA.104.504167.
43. Sun J, Underhill HR, Hippe DS, Xue Y, Yuan C, Hatsukami TS. Sustained acceleration in carotid atherosclerotic plaque progression with intraplaque hemorrhage: a long-term time course study. *JACC Cardiovasc Imaging*. 2012;5:798–804. doi: 10.1016/j.jcmg.2012.03.014.
44. Lin J, Kakkar V, Lu X. Impact of matrix metalloproteinases on atherosclerosis. *Curr Drug Targets*. 2014;15:442–453.
45. Shah PK. Biomarkers of plaque instability. *Curr Cardiol Rep*. 2014;16:547. doi: 10.1007/s11886-014-0547-7.
46. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events. *J Am Coll Cardiol*. In press.