The search to find the location of future plaque ruptures or plaque erosions leading to myocardial infarction (so-called “vulnerable plaques”) is an important area of cardiovascular research. Systemic therapy, including use of statins, targets the vulnerable patient. However, adverse events cannot be completely eliminated with the appropriate application of systemic therapies and thus has given rise to the possibility of local or regional therapy of “vulnerable plaques” to prevent future events. Until now, no criteria have been developed for consideration of this therapy. For such a strategy to work, there should be several prerequisites. These involve the identification of susceptible lesions, the number of lesions, their natural history, and proof that an interventional technique is preferable to medical therapy alone. The greatest deficiency relates to the fact that until the natural history of presumed “vulnerable plaques” is known one can never truly identify what constitutes a “vulnerable plaque.” Much work needs to be done in this area, but ongoing and new trials should provide important information that could potentially change drastically how coronary artery disease is diagnosed and treated. (J Am Coll Cardiol 2008;51:1539–42) © 2008 by the American College of Cardiology Foundation
A “vulnerable plaque” caused by plaque erosion should be identifiable. For a local technique to be completely effective, all lesions responsible for MI should be identifiable. At least one-third of lesions responsible for major coronary thrombi on pathologic analysis are secondary to plaque erosions (15). Because the underlying plaque is not necessarily lipid-rich, inflamed, or possessing a thin cap, the techniques already described might not identify such lesions. Increased coagulability of the blood, the presumed mechanism most likely responsible for or associated with plaque erosions, might not target specific lesions that are easily identifiable by the aforementioned techniques. Thus, MIs caused by plaque erosions (or any lesion other than a TCFA) have not been a specific target for those who are attempting to identify “vulnerable plaques” before an event.

The least frequent histologic plaque associated with thrombosis is a calcified nodule and is seen in up to 10% of culprit thrombosed plaques on autopsy (16). Although other types of “vulnerable plaques” have been proposed (17), the 3 aforementioned (TCFA, erosions, and nodules) are considered by consensus to account for nearly all major coronary thrombi at autopsy (16). No vulnerable plaque detector is presently addressing the calcified nodule.

The number of “vulnerable plaques” is known, and the number is limited. For a local/regional approach to be feasible, the number must be limited and, if not limited by number, “vulnerable plaques” should be limited to specific areas of the coronary artery that can be effectively treated. Several in vivo studies have tried to evaluate the number of presumed “vulnerable plaques” with IVUS, angioscopy, or OCT (18–20). Pathologic studies have also been used to identify the number of TCFA in patients dying from coronary or noncoronary events. Several in vivo studies have identified various types of lesions, including ruptured asymptomatic plaques with IVUS, yellow (lipid-rich) plaques with angioscopy, and intact, thin-capped lesions with OCT. Most studies suggest there are no more than 2 to 3 such lesions/patient even in those presenting with MI in another vessel or at another site (21).

There is, however, a fundamental flaw in this research. Without natural history studies, no one really knows what a “vulnerable plaque” looks like. Pathologic studies have shown us the characteristics of the culprit plaques responsible for MI or sudden coronary death. These are already ruptured plaques containing intracoronary thrombus. The “vulnerable plaque” before an event could be a TCFA with an intact cap. Yet, how much plaque lipid, necrotic core, or inflammation is needed? And how thin must the cap be to call it vulnerable on an initial evaluation? Another potential candidate for a “vulnerable plaque” might be an already ruptured but asymptomatic plaque such as those detected by IVUS at nonculprit sites from patients undergoing intervention with an acute syndrome. Until the proper long-term studies have been performed, this is in my opinion the most critical deficiency for those attempting to identify and therapeutically alter “vulnerable plaque” (Fig. 1).

The natural history of a “vulnerable plaque” has been identified in patients treated with optimal systemic therapies. As mentioned earlier, only with natural history studies will one ever hope to understand what constitutes “vulnerable plaque.” Furthermore, these studies must assess through long-term follow-up the propensity for such plaques to develop a hard cardiovascular end point (vide infra) in patients receiving optimum systemic therapies, including aspirin, statins to an optimum low-density lipoprotein cholesterol level, and the use of appropriate doses of angiotensin-converting enzyme inhibitors and beta blockers (22). Such natural history studies as described in the preceding text must be large, prospective, and follow-up all potential “vulnerable plaques,” particularly those that remain asymptomatic on follow-up. Initial and follow-up studies must use various imaging techniques to identify presumed “vulnerable plaques.” Ongoing natural history studies such as PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) will soon report their initial results. However, asymptomatic patients will not undergo repeat imaging and therefore this study can not answer all important issues related to natural history of presumed vulnerable lesions.

Ideally, natural history studies should last for several years and target high-risk patients, such as in the PROSPECT trial. Trials would be greatly facilitated by a noninvasive technique to serially follow and identify “vulnerable plaque.” Unfortunately, such a technique is not presently available. Whatever technique is shown to identify a true “vulnerable plaque” on natural history, it must also have a very high sensitivity and specificity.

An interventional approach applied locally or regionally to an asymptomatic “vulnerable plaque” is proven to reduce future events relative to the best systemic medical therapy. For a local/regional approach to an otherwise asymptomatic plaque to be effective, what should the therapy consist of? Of course, it must be safer and more effective in reducing events than the best medical therapies available.

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**Table 1** Prerequisites for a Local or Regional Approach to “Vulnerable Plaque”

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. “Vulnerable plaque” caused by a thin-capped fibroatheroma can be identified</td>
<td>with modern technology.</td>
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<tr>
<td>2. A “vulnerable plaque” caused by plaque erosion should be identifiable.</td>
<td></td>
</tr>
<tr>
<td>3. The number of “vulnerable plaques” is known, and the number is limited.</td>
<td></td>
</tr>
<tr>
<td>4. The natural history of a “vulnerable plaque” has been identified in patients</td>
<td>treated with optimal systemic therapies.</td>
</tr>
<tr>
<td>5. An interventional approach applied locally or regionally to an asymptomatic</td>
<td>“vulnerable plaque” is proven to reduce future events relative to the best systemic medical therapy.</td>
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Presently, there is no ideal interventional technique for such asymptomatic plaques. Perhaps, newer generations of drug-eluting stents (bioabsorbable stents?) could be the answer, but superiority over optimal medical therapy alone will have to be proven in a very large randomized trial (23). A trial such as this must have as its primary end point only hard cardiovascular events, including fatal and nonfatal acute MI and definite unstable angina, because these are most likely to be caused by disruption/thrombosis of vulnerable lesions (22).

Furthermore, these studies will be complicated by the likelihood of a cardiac event for a proven “vulnerable plaque.” For example, if natural history studies indicate that only 5% of a given plaque type as identified will develop an event on follow-up (number needed to treat [NNT] = 20), all 20 of these plaques will need to be treated with a new and expensive procedure to prevent 1 event. What are the consequences? If, however, the NNT to prevent a cardiac event is low at, for example, ≤5, then a procedure on all of these plaques could make sense. These and other questions will need to be addressed in future trials.

Conclusions

The search for the “vulnerable plaque” and evidence-based proof that a local or regional approach will successfully reduce events will be extremely difficult and time-consuming, requiring several years of natural history and therapeutic trials. On the basis of the 5 prerequisites, at present, only the first is possible and the other 4 require further study. Even if the site of a future plaque erosion cannot be identified, fulfilling the other criteria could provide data to support a focal approach to other “vulnerable plaques,” such as the TCFA. Although the process to prove efficacy will be daunting, appropriately sized and well-designed trials should add vital information about the pathophysiology of coronary artery disease and could change profoundly how coronary artery disease is diagnosed and treated.

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REFERENCES


