

# Acute coronary syndromes: from treatment to prevention

## The enduring challenge of vulnerable plaque detection in the cardiac catheterization laboratory

**Marco Valgimigli, MD; Gastón A. Rodriguez-Granillo, MD; Pierfrancesco Agostoni, MD; Patrick Serruys, MD, PhD**

ThoraxCenter - Erasmus MC - Rotterdam - THE NETHERLANDS

*Rupture of vulnerable plaques is the main cause of acute coronary syndromes. Identification of such plaques is therefore essential to develop treatment modalities to stabilize them. Several intravascular technologies are described in this review. The ideal technique would provide morphological, mechanical, and biochemical information; although several imaging techniques are currently under development, none of them provides, alone, such all-embracing assessment. Optical coherence tomography has the advantage of high resolution, thermography has the potential to measure metabolism, and Raman spectroscopy obtains information on chemical components. Intravascular ultrasound (IVUS) and IVUS-palpography are easy to perform, and assess morphology and mechanical instability. Shear stress is an important mechanical parameter that deeply influences vascular biology. Nevertheless, at present, each technique generally only assesses one clinical feature, so that none of them can unequivocally and comprehensively identify a vulnerable plaque nor predict its further development. Thus, the combination of several modalities is required to ensure high sensitivity and specificity in detecting vulnerable plaques.*

**Keywords:** acute coronary syndrome; myocardial infarction; vulnerable plaque; imaging; treatment; prevention

**Address for correspondence:** Prof Patrick Serruys, ThoraxCenter, Erasmus MC Rotterdam, Room BD 404, Postbus 2040, CA Rotterdam, NL-3000, The Netherlands (e-mail: p.w.j.c.serruys@erasmusmc.nl)

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Plaque rupture, platelet activation, and thrombus formation are recognized as key events in the pathogenesis of acute coronary syndromes (ACS). The ability of aspirin to reduce recurrent ischemic events in ACS has been clearly and consistently demonstrated in the last decades, and this has progressively led to an increasing effort to control and block platelet activation when plaque rupture occurs, either spontaneously, during an ACS, or during percutaneous coronary intervention (PCI).

The introduction of potent antiplatelet agents, such as the glycoprotein IIb/IIIa inhibitors, has further reduced the rate of major cardiac adverse events as compared with aspirin and heparin alone, strongly supporting the notion that platelet reactivity is pivotal in the pathogenesis of complications related to plaque rupture, and progressive refinements of antiplatelet treatment will significantly improve outcome in patients suffering from ACS. However, in the last years, focus has progressively shifted from treatment to prevention, mainly driven by a comprehensive approach based on systemic

### SELECTED ABBREVIATIONS AND ACRONYMS

<b>ACS</b>	acute coronary syndrome
<b>ANGUS</b>	angiography and intravascular ultrasound
<b>IBIS</b>	Integrated Biomarkers and Imaging Study
<b>IVUS</b>	intravascular ultrasound
<b>MI</b>	myocardial infarction
<b>OCT</b>	optical coherence tomography
<b>PCI</b>	percutaneous coronary intervention
<b>TCFA</b>	thin-cap fibroatheroma

therapy, such as use of statins and angiotensin-converting enzyme (ACE) inhibitors coupled with vulnerable plaque detection and “passivation” (the complex process of stabilizing the active plaque at risk of rupture) by means of locally delivered therapy.<sup>1-5</sup>

Before the concept of plaque sealing (by coronary balloon angioplasty or stenting) is tested in terms of efficacy and cost-effectiveness, however, we need to provide clinicians with tool(s) able to consistently and reliably detect vulnerable coronary plaques. The challenge for the future is to identify vulnerable plaques before the thrombus forms. The current review focuses on invasive imaging potentially able to identify hot plaques having recently undergone rupture or prone to rupture.

### THE VULNERABLE PLAQUE

A wide variety exists in the structure and function of coronary atherosclerotic plaques. Most plaques may cause no symptoms for decades; however, a few plaques disrupt and cause thrombosis. These rare, but dangerous, thrombosis-prone plaques are termed vulnerable.<sup>6</sup> Thus, a vulnerable plaque is a plaque assumed to be at high short-term risk of thrombosis, resulting in an ACS.

There are three forms of vulnerable plaques, all documented by pathologic studies:

- *Thin-cap fibroatheroma (TCFA)*: in about 65% of all symptomatic coronary thrombotic events, rupture of an inflamed TCFA is evident. The major components of such TCFA are: an atheromatous core (usually >40% of the entire plaque), a thin fibrous cap with macrophage and lymphocyte infiltration and decreased smooth muscle cell content, and expansive remodeling.<sup>7</sup>
- *Erosion*: in about 30% of all events, the endothelium overlying the plaque has been found injured at the place where a thrombus has formed. Usually, these plaques are rich in proteoglycans.<sup>8</sup>
- *A calcified nodule*: in 5% of all events, thrombosis covering a calcified nodule suggests that the plaque is heavily calcified, with a calcified nodule projecting into the lumen.<sup>9</sup>

The terms vulnerable plaque, high-risk plaque, and thrombosis-prone plaque can be used identically.<sup>6</sup> Currently, there is no widely accepted diagnostic method to prospectively identify such vulnerable plaques. Many of the imaging techniques used to assess coronary artery disease are able to detect different features of the rupture-prone type of vulnerable plaques.

### ANGIOGRAPHY

Coronary angiography has been so far the gold standard to assess the severity of obstructive luminal narrowing. Furthermore, it serves as a decision tool to direct therapy such as PCI or coronary artery bypass surgery (CABG). Using coronary angiography, we can assess the lumen boundaries, but no information is given on plaque burden, plaque delineation, and plaque components. Actually, angiography is able to detect complex lesions, which are considered vulnerable plaques at an advanced stage. Complex lesions have some peculiar angiographic features: intraluminal filling defects (consistent with thrombus), presence of contrast and hazy contour beyond the vessel lumen (consistent with plaque ulceration), irregular margins and overhanging edges (consistent with plaque irregularity and, possibly, fracture) and impaired flow with evident lumen reduction.<sup>10</sup> The presence of multiple complex lesions in patients after a myocardial infarction (MI) has been associated with increased incidence of ACS.<sup>10</sup> However, angiography is a crude technique to assess the presence and burden of vulnerable lesions, as the majority of ulcerated plaques are not big enough to be detected by angiography, but can be well assessed pathologically.<sup>11</sup> Indeed, about 70% of acute coronary occlusions are in areas that were previously angiographically normal, and only a minority occurs where there was severe stenosis.<sup>12,13</sup> Furthermore, we have to take into account that the predictive power of angiography is strongly dependent on the time interval between the angiogram and MI, because both time and interim therapy can influence atherosclerosis. In one study, the angiograms were performed between 1 and 77 months before the event<sup>13</sup> and showed that atherosclerosis can be a rapidly progressive process. Another study evaluated angiograms performed 1 week before acute MI showing that signs of thrombosis and rupture were present in the majority of patients.<sup>14</sup> Thus, patients with silent nonobstructive coronary atherosclerosis harbor vulnerable plaques that cannot be detected by angiograms, but are associated with adverse clinical outcomes. If a disrupted ulcerated plaque is seen on angiography (*Figure 1*), the existence of additional rupture-prone plaques is to be expected. Angiography therefore has a low discriminatory power to identify the vulnerable plaque.

### ANGIOSCOPY

Angioscopy uses fiber optics to visualize thrombi and plaque surface (*Figure 2*). Vulnerable plaque features, such as ruptured caps and red discoloration

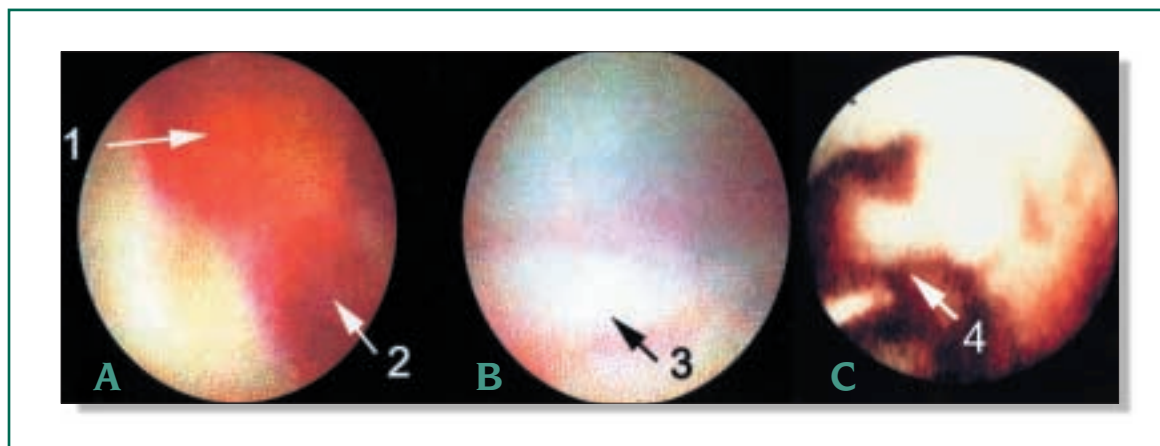


**Figure 1.** Angiography reveals a dissected flap within the lumen, indicating a ruptured plaque.

(intraplaque hemorrhage), can be detected. In patients with acute MI, angioscopy showed diffuse disease in all the three coronary arteries, with multiple yellow plaques.<sup>15</sup> Furthermore, in a 12-month follow-up study of patients with stable angina, ACS occurred more frequently in patients with yellow plaques than in those with white plaques.<sup>16</sup> These results suggest that yellow plaques, which may be visualized by angioscopy, but not by angiography, may be more prone to rupture than white plaques. However, this technique has several drawbacks. Indeed, only a limited part of the vessel tree can be investigated, due to the size of the device. Furthermore, information about the degree of plaque extension into the vessel wall is not provided. Finally, to enable clear visualization of the vessel wall, the vessel has to be occluded and the remaining blood flushed away with saline, thereby potentially inducing ischemia.

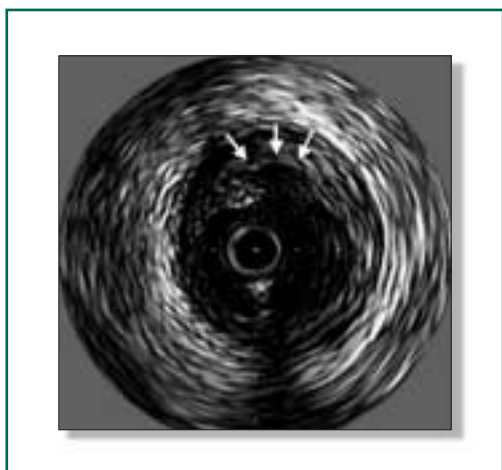
## INTRAVASCULAR ULTRASOUND

Intravascular coronary ultrasound (IVUS) provides real-time high-resolution images of the vessel wall and lumen. Depending on the distance of the vessel wall from the catheter, the axial resolution is about 150 microns, the lateral 300 microns. The images appear in real time. Features of the vessel can be detected based on the echogenicity of different tissue types. Small structures can be visualized, however only those sized over 160 microns can be estimated accurately. The normal thickness of the media is about 125 to 350  $\mu\text{m}$ . IVUS provides some insight into the composition of coronary plaques. In IVUS images, calcification is characterized by a bright echo signal with distal shadowing that hides plaque components and deeper vessel structures. In comparative studies between histology and IVUS, plaque calcification can be detected with a sensitivity of between 86% and 97%.<sup>17</sup> The sensitivity to detect microcalcification ranges around 60%.<sup>18</sup> In IVUS images, lipid depositions are described as echolucent zones and can be detected with a sensitivity of between 78% and 95% and specificity of 30%.<sup>19</sup> This sensitivity is dependent on the amount of lipid and can drop down further if the echolucent area is smaller than a quarter of the plaque. Echolucent zones can also be caused by loose tissue and shadowing from calcium, which makes the interpretation of these areas difficult. The sensitivity to differentiate between fibrous and fatty tissue is between 39% and 52%.<sup>20</sup> The detection of vulnerable plaques by IVUS is mainly based on a series of case reports. The main focus of these reports is the detection of already ruptured plaques. To evaluate the role of IVUS in detecting plaque rupture, a study was performed in patients with angina. Ruptured plaques were characterized by a cavity (echolucent area



**Figure 2.** Angioscopy shows: (A) a red thrombus on a plaque (1), blocking a part of the lumen (2). After removal of thrombus and plaque with atherectomy (B) a white flap is visible (3). Postangioplasty angioscopy (C) can show a dissecting flap (4) within the lumen.

within the plaque) and a tear of the thin fibrous cap (*Figure 3*). Plaque rupture was confirmed by an injection of contrast medium with subsequent filling of the plaque cavity, seen on IVUS. Ruptured plaques were identified in 74% of patients presenting with unstable angina. Of the patients without plaque rupture, only 18% had unstable angina. The echolucent area (cavity)–to–total plaque area ratio was larger in the unstable group than in the stable group. The thickness of the fibrous cap in the unstable group was also found to be smaller than in the stable group.<sup>21</sup> Other studies have shown that multiple plaque ruptures may be diffusely present in all the coronary arteries of patients with ACS,<sup>22</sup> but not all of them produce symptoms. Indeed, plaque ruptures causing acute symptoms were associated with a smaller minimum lumen area and a greater thrombotic burden.<sup>23</sup> Major limitations of these



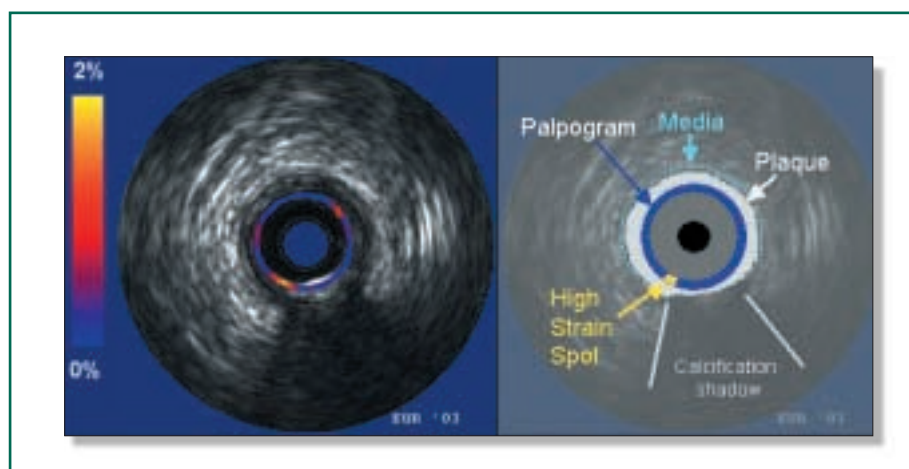
**Figure 3.** The intravascular ultrasound cross-section shows an eccentric ruptured plaque with deep ulcer (**arrows**). A thin flap is still covering parts of the ulceration. Courtesy of Paul Schoenhagen.

studies are their retrospective nature and the lack of follow-up. Only Yamagishi et al have performed a prospective study with a follow-up period of about 2 years. Large eccentric plaques containing an echolucent zone by IVUS were found to be at increased risk of instability even though the lumen area was preserved at the time of initial study.<sup>24</sup> IVUS assessment of vascular remodeling may help to classify plaques with the highest probability of spontaneous rupture. It has been demonstrated that ruptured plaques are associated with positive remodeling.<sup>25</sup> A number of groups have investigated the potential of ultrasound radio-frequency signal analysis for tissue characterization.<sup>26,27</sup> In particular, virtual histology is the first attempt at detailed tissue characterization. This technique is based on backscatter analysis of the radio-frequency

signals produced by the IVUS unit. Spectral parameters derived from the backscatter analysis are used to develop classification schemes, which allow differentiation between four general tissue types (lipid, lipid-fibrous, calcified, calcified-necrotic), validated by ex vivo histology.<sup>28</sup> The value of this technique is being currently tested in several clinical trials.

### INTRAVASCULAR ELASTOGRAPHY/PALPOGRAPHY

In 1991, a new technique was introduced to measure the mechanical properties of tissue using ultrasound—elastography.<sup>29</sup> The underlying concept is that upon uniform loading, the local relative amount of deformation (strain) of a tissue is related to the local mechanical properties of that tissue. If we apply this concept to determine the local properties of arterial tissue, blood pressure acts as a stressor. At a given pressure difference, soft plaque components will deform more than hard components. Measurement of local plaque deformation in the radial direction can be obtained with ultrasound. In vitro studies with histologic confirmation have shown that there are differences of strain normalized to pressure between fibrous, fibro-fatty, and fatty components of the plaque of coronary as well as femoral arteries.<sup>30</sup> This difference was mainly evident between fibrous and fatty tissue. Interestingly, these plaque types could not be differentiated by echo-intensity differences on the IVUS echogram. In another in vitro study, postmortem coronary arteries were investigated with elastography and then processed for histology. The sensitivity and specificity of elastography to detect TCFA were, respectively, 88% and 89%. Furthermore, there was a high correlation between the strain in the cap and the amount of macrophages.<sup>31</sup> For intravascular purposes, a derivative of elastography called palpography may be a suitable tool.<sup>32</sup> In this approach, one strain value per angle is determined and plotted as a color-coded contour at the lumen vessel boundary. Since radial strain is obtained, the technique may have the potential to detect regions with elevated stress: increased circumferential stress results in an increased radial deformation of the plaque components. It is feasible to apply intravascular palpography during catheterization procedures. The systemic pressure is used to strain the tissue, and the strain is determined using cross-correlation analysis of sequential frames acquired at different pressures. A likelihood function is determined to obtain the frames with minimal motion of the catheter in the lumen since motion of the catheter impairs accuracy of strain estimation. Minimal motion is mainly observed near the



**Figure 4.** The palpogram shows an eccentric plaque with a big calcification. On the left shoulder there is a high-strain spot of an otherwise less deformable plaque, probably representing a vulnerable plaque.

end of the passive filling phase. Reproducible strain estimates are obtained within one pressure cycle and over several pressure cycles. Palpography has been shown to detect, in human coronary arteries, strain patterns typical of deformable plaques (*Figure 4*). Furthermore, the number of deformable plaques per patient correlated positively with the clinical presentation and with the serum level of C-reactive protein.<sup>33</sup> Palpography provides additional information to IVUS. The differentiation between hard and soft tissue may be important for the detection of a vulnerable plaque. Since palpography is based on clinically available IVUS catheters, the technique can be easily introduced into the catheterization laboratory. The clinical value of this technique is currently under investigation in the Integrated Biomarkers and Imaging Study (IBIS).

### THERMOGRAPHY

Since atherosclerosis is an inflammatory disease<sup>34</sup> and inflammation determines an elevation in temperature, hypothetically, a temperature rise should be measured at the surface of a plaque. Furthermore, as vulnerable plaque is a very active metabolic area, it has been postulated that even higher temperature could be found due to heat released by activated macrophages either on the plaque surface or under a thin cap. The pioneering paper by Casscells et al reported that carotid plaques taken at endarterectomy have temperature heterogeneity. The temperature difference (measured outside the body, at room temperature) between different areas was up to 2.2°C, and correlated with cell density (mainly macrophages).<sup>35</sup> Stefanadis et al performed studies in human patients with stable angina, unstable angina, and acute MI. Temperature was constant within the arteries of the control subjects, whereas most atherosclerotic plaques showed higher

temperatures compared with healthy vessel wall. Temperature differences between atherosclerotic plaque and healthy vessel wall increased progressively from stable angina to acute MI with a maximum difference of  $1.5 \pm 0.7^\circ\text{C}$ .<sup>36</sup> Furthermore, a high temperature gradient ( $>0.5^\circ\text{C}$ ) between the atherosclerotic plaque in the culprit vessel and the healthy vessel wall was shown to be an independent predictor of adverse events after PCI.<sup>37</sup> These data have yet to be confirmed prospectively in other centers, and the influence of parameters such as coronary blood flow or catheter design has to be studied in the future.

### OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) can provide images with ultrahigh resolution. The technique measures the intensity of back-reflected light in a similar way as IVUS measures acoustic waves. Light is split into two signals: one is sent into the tissue and the other to a reference arm with a mirror. Both signals are reflected and cross-correlated by interfering the light beams. To achieve cross-correlation at incremental penetration depths in the tissue, the mirror is dynamically translated. The intensity of the interfering signals at a certain mirror position represents backscattering at a corresponding depth. Images with an extremely high resolution, ranging from 4 to 20  $\mu\text{m}$ , can be achieved with a penetration depth up to 2 mm. Images can be acquired in real time (*Figure 5, page 146*). Early attempts were made to validate OCT using histology. A lipid pool generates decreased signal areas with poorly delineated borders, a fibrocalcific plaque shows a sharply delineated region with a signal-poor interior, and a fibrous plaque produces a homogenous signal-rich lesion.<sup>38</sup> The first in vivo comparison of OCT with IVUS demonstrated superior delineation by OCT of



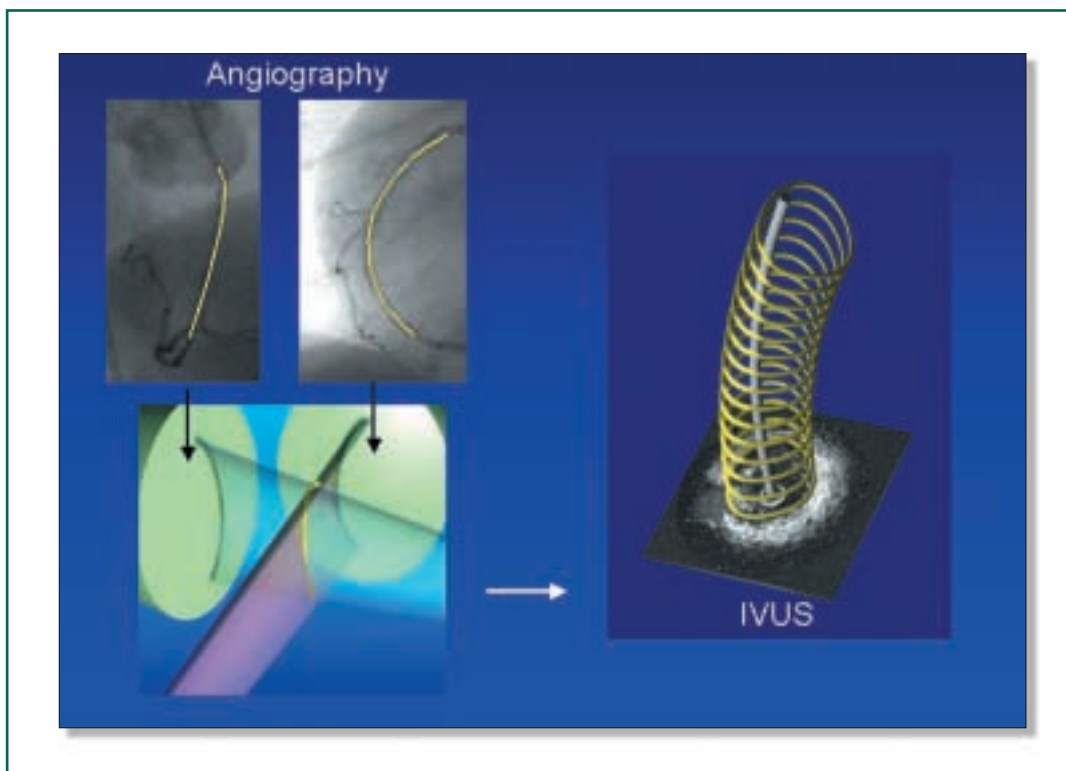
**Figure 5.** Optical coherence tomography produces high-resolution, real-time, cross-sectional, or 3-D images of tissues at an exceptionally high, histology-like resolution of a eccentric plaque with a thin cap (arrows). Courtesy of Evelyn Regar.

structural details like thin caps or tissue proliferation.<sup>39</sup> However, OCT has several limitations: the low penetration depth, which hinders studying large vessels, and the light absorbance by blood, which currently needs to be overcome by saline infusion or balloon occlusion with associated potential for ischemia.

## SPECTROSCOPY

Using fiber-optic technology, coronary plaques can be illuminated in situ and the reflected light can be collected and launched into a spectrometer. Spectroscopy is based on the property that different chemical compounds absorb and scatter different amounts of energy at different wavelengths, so each tissue, due to its chemical composition (lipid, collagen, calcium, etc), has a unique pattern of light absorbance, leaving a unique chemical (molecular) fingerprint. Different approaches are under development. Raman spectroscopy\* uses high-energy laser light, it has a high molecular sensitivity, but its tissue penetration is as low as 0.3 mm. Near-infrared (NIR) spectroscopy (with wavelengths from 750 to 2500 nm) has greater penetration (2 mm), but lower molecular sensitivity and therefore relies on pattern recognition for plaque typing. Intracoronary spectroscopy has not yet been tested clinically.<sup>40</sup>

\*based on the the Raman effect, discovered by the Indian physicist C. V. Raman in 1928: when incident photons interact with a molecular system, most are elastically scattered (in a process called "Rayleigh scattering," in which incident photons have the same energy as the scattered photons), while only a small fraction of photons (about 1 in 107) are inelastically scattered ("Raman scattering", in which the energies of the incident and scattered photons are different).



**Figure 6.** 3-D reconstruction technique combining ANGIography and intravascular ultrasound (IVUS) allowing an exact reconstruction of the vessel shape.



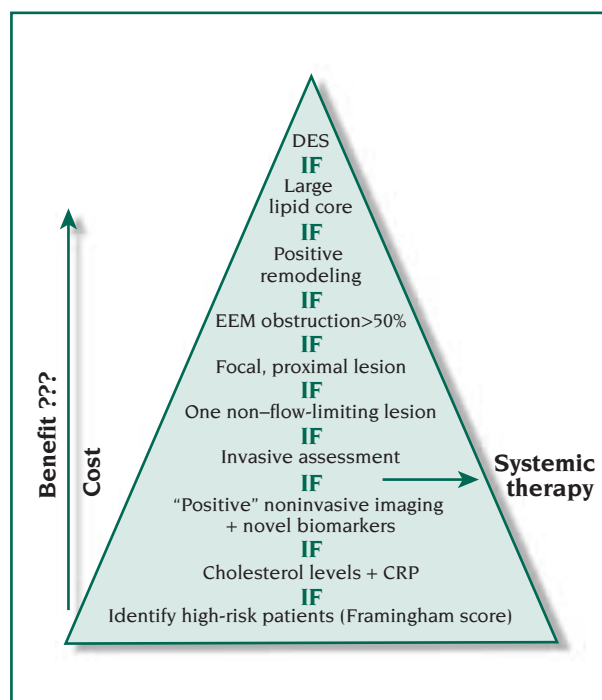
## ANGUS AND SHEAR STRESS

High-resolution reconstruction of three-dimensional (3-D) coronary lumen and wall morphology is obtained by combining angiography and IVUS.<sup>41</sup> Briefly, a bi-plane angiogram of a sheath-based IVUS catheter taken at end-diastole allows reconstruction of the 3-D pull-back trajectory of the catheter. Combining this path with lumen and wall information derived from IVUS images that are successively acquired during catheter pullback at end-diastole gives accurate 3-D lumen and wall reconstruction with resolution determined by IVUS (Figure 6). The use of computation flow dynamics allows calculation of detailed blood velocity profile in the lumen and shear stress on the vessel walls.<sup>42</sup> For this purpose, absolute flow and blood viscosity need to be provided as boundary conditions. From the blood velocity profile local wall shear stress on the endothelium can be accurately derived. Wall shear stress is the frictional force, normalized to surface area, that is induced by the blood passing the wall. Although from a mechanical point of view shear stress is of a very small magnitude compared with blood pressure-induced tensile stress, it has a profound influence on vascular biology and explains the localization of atherosclerotic plaque in the presence of systemic risk factors. Many of these biological processes also influence the stability of the vulnerable plaque, including inflammation, thrombogenicity, vessel remodeling, intimal thickening, or regression, and smooth muscle cell proliferation. Therefore, the study of this parameter as derived by image-based modeling is of utmost importance.

## CONCLUSION

Assessment of atherosclerosis by imaging techniques is essential for in vivo identification of vulnerable plaques. The ideal technique would provide morphological, mechanical, and biochemical information; however, in spite of the fact that several imaging techniques are currently under development, none of them provides alone such all-embracing assessment.

OCT has the advantage of high resolution, thermography has the potential to measure metabolism, and spectroscopy obtains information on chemical components. IVUS and IVUS-palpography are easy to perform and assess morphology and mechanical instability. Shear stress is an important mechanical parameter that deeply influences vascular biology. Nevertheless, all techniques are still under investigation and, at present,



**Figure 7.** The hypothetical pyramid of clinical decision-making on how to treat a vulnerable plaque. If all conditions are satisfied, including the fact that a patient is already receiving an invasive procedure due to other flow-limiting lesion(s), the preventive local treatment of a potential vulnerable plaque may be potentially considered. However, it should be always kept in mind that this strategy has never been tested prospectively.

**Abbreviations:** CRP, C-reactive protein; DES, drug-eluting stent; EEM, external elastic membrane.

none of them can completely identify a vulnerable plaque and, most importantly, predict its further development. This is related to fundamental methodological insufficiencies that may be resolved in the future. From a clinical point of view, most techniques currently assess only one feature of the vulnerable plaque. Thus, the combination of several modalities will be of importance in the future to ensure a high sensitivity and specificity in detecting vulnerable plaques. To conclude, a hypothetical clinical decision-making tree is presented in Figure 7. If all conditions are satisfied, then it is probably logical to try to treat the vulnerable plaque with a local treatment (plaque sealing) in the attempt to prevent the consequences related to its possible rupture or erosion. In any event, this strategy has never been tested prospectively and it should be never forgotten that the restenosis rate—even in the drug-eluting stent era—is not equal to zero.

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