Several independent lines of clinical evidence have shown that critical stenoses cause only a fraction of ACS. Rather, ruptures of a thin fibrous cap covering a large lipid-rich necrotic or superficial intimal erosion frequently trigger acute coronary thromboses at sites of non-critical narrowing of coronary arteries. This shift in thinking has fostered the notion of the so-called ‘vulnerable’ or ‘high-risk’ plaque and spawned manifold attempts to develop methods for detection of the vulnerable plaque, 4 a quest predicated on the postulate that local intervention could preclude plaque thrombosis and possibly prevent ACS. Indeed, this approach may prove applicable in patients already targeted for invasive diagnosis or treatment in whom identification of non-stenotic lesions unseen by traditional angiography might guide a local intervention aimed at future coronary event prevention. Patients presenting with ACS are at a particularly high short-term risk of recurrence and this justifies such an aggressive approach.

Rapidly accumulating clinical data suggest that a search to identify a single vulnerable plaque to guide local therapy may seriously underestimate the complexity of the challenge. Indeed, this issue is further complicated by the fact that coronary plaque erosion without any rupture of a lipid core is a frequent cause of coronary thrombosis and sudden coronary death. Although topographic correlation has been shown between the presence of an inflammatory infiltrate and the site of plaque rupture and thrombosis, different pathological observations support the concept that plaque vulnerability and adverse outcome are not only related to a localised vascular accident but a reflection of a more generalised pathophysiological process of diffuse involvement of the entire coronary tree. Patients whose burden of disease includes flow-limiting stenoses usually harbour diffuse but angiographically unseen disease along the length of their arteries. The concept of ‘patient vulnerability’ in ACS is suggested by numerous clinical studies showing increased acute-phase reactants in the serum of patients with unstable angina and those at risk of future myocardial infarction (MI). The major predictors of plaque progression have been recognised to be multivessel disease, prior PCI and age less than 65 years.

Although these observations underscore the need for identifying those multiple dangerous plaques in high-risk-profile patients who will benefit from early prophylactic intervention, the question remains how this evidence should improve practice. Clearly, early invasive management, including local intervention on the culprit lesion in conjunction with contemporary systemic therapy can improve outcomes of many patients affected by ACS. Still, recurrent cardiovascular events in this population remain unacceptably high. Therefore, in addition to angiography, ready-available, high-resolution imaging modalities are needed to improve the search and recognition of high-risk plaques.

VH-IVUS and Other Modalities for Vulnerable Plaque Imaging

Various imaging techniques are currently under investigation by extensive clinical testing to identify which could become the most sensible and specific modality for vulnerable plaque detection. Non-invasive imaging, such as computed tomography (CT), is overcoming motion artefacts with the use of multi-detector rows, ultra-thin slices and increased gantry speeds. CT has shown limited success using ex vivo histology of peripheral arteries in identifying high-risk plaques such thin-cap atheroma (TCFA), and is of limited use in calcified arteries, which is a significant drawback. Magnetic resonance imaging (MRI) holds promise as recent advances in hardware and pulse sequences have improved signal-to-noise ratio, allowing resolution of ≤400mm. However, the distance between the coil and the coronary vasculature, tortuosity of vessels and motion effects limit usefulness to the major epicardial arteries.

The emerging technologies with the greatest resolution are indeed catheter-based and many intravascular modalities have been developed for...
identification of TCFA. Optical coherence tomography (OCT) offers resolution as fine as 10µm. Furthermore, acquisition rates are high, and there are no transducers within the catheters. However, attenuation by blood and surface foam cells and lack of penetration of deeper regions of plaque remain obstacles to the current utilisation of OCT as a diagnostic tool.

Greyscale images obtained with intravascular ultrasound (IVUS) derive from the analysis of echoes amplitude or intensity. However, the vulnerable plaque characteristics reported by greyscale IVUS have differed from study to study, and non-culprit plaques in stable patients have often been found to show the same plaque morphological components associated with vulnerable plaque, thereby casting uncertainty on the ability of IVUS to identify plaques susceptible to rupture, fissure or erosion. In addition, IVUS resolution is too low to detect thin fibrous caps (50–75µm), typical feature of vulnerable plaques. The 2-D IVUS image, derived from ultrasound frequencies in the range of 20–40MHz, results in an axial resolution of 100–200µm and a lateral resolution of 250µm. These properties, though beneficial for visualising deep structures, limit imaging of microstructures, like thin fibrous cap, yielding a sensitivity of only 37% for the detection of plaque rupture.

IVUS-Virtual Histology™ (IVUS-VH) is the most promising technique in the field. IVUS-VH offers an in vivo opportunity to assess plaque morphology. VH-IVUS uses underlying frequency information along with echoes intensity, while IVUS data are obtained from echoes of different intensity or amplitude. Based on tissue maps, colour codes have been assigned to a specific spectrum of the radiofrequency signal and different tissue components characterised as fibrous (labelled green), fibro fatty (labelled greenish yellow), necrotic core (NC) (labelled red) and calcium. Indeed, IVUS-VH technology has been shown to have a 93–99% in vivo accuracy when used to identify the four different types of atherosclerotic plaques. Moreover, correlation of in vivo IVUS-VH data analysis with histopathology shows a high accuracy.

The major advantage of IVUS-VH is that it is based on a device that is practical for use in the clinical setting and that it generates a realtime assessment of plaque morphology. However, because this technology is based on IVUS with a maximum radial resolution of 100µm, it cannot evaluate the presence or absence of a thin fibrous cap. Although the most accepted threshold to define a cap as ‘thin’ has been set at 65µm by pathology investigations, a number of important ex vivo studies have used higher (>200µm) thresholds. Indeed, one of these studies identified a mean cap thickness of 260µm and 360µm for vulnerable and non-vulnerable plaques, respectively. Because the axial resolution of IVUS-VH is between 100µm and 150µm, it is assumed that the absence of visible fibrous tissue overlying a necrotic core suggested a cap thickness below 100–150µm and used the absence of such tissue to define a thin fibrous cap. Utilising VH-IVUS a classification of different plaque types (from stable to unstable) has been also proposed (see Figure 1).

Establish the Natural History of High-risk Vulnerable Plaques

Identification of lesions with morphological characteristics of vulnerable plaques is not sufficient; the natural history of these lesions need to be observed and the hypothesis of their potential clinical instability confirmed. Only prospective observation could reliably identify which plaque is prone to rupture and change the approach to the treatment of coronary atherosclerotic disease.

In this setting, the Providing Regional Observation to Study Predictors of Events in the Coronary Tree (PROSPECT) trial will determine the likelihood and probabilities of specific plaques, with typical IVUS-VH morphology, of causing clinical events. The multicentre European/US trial has enrolled 700 patients presenting with ACS (UA, non-STEMI) or ST-elevation MI (STEMI) >24h). After successful PCI of the culprit lesion patients will receive a three-vessel imaging of the first 6–8cm from the ostium with the use of angiography, IVUS-VH and palpography (only for 350 patients). Clinical follow-up is scheduled every year for five years or event-driven with re-angiography for patients with clinical events. Patient enrolment is completed and preliminary results will be presented in future meetings.

Another study, Study of Prospective Events in Coronary Intermediate Atherosclerotic Lesions (SPECIAL), will utilise greyscale IVUS and VH-IVUS imaging technology to collect data about characteristics of lesions not causing symptoms at the time of treatment. Additionally, in a large-scale natural history of atherosclerosis trial, 1,000 patients will have IVUS and VH-IVUS imaging 12 months after their initial intervention and examination. The study will correlate lesion characteristics, patient risk factors and other measurements with subsequent heart attacks and other cardiac events as well as plaque progression and regression. The Volcano VH Registry is a global multicentre...
registry with more than 40 participating sites that has enrolled over 2,500 patients so far. The objective is to correlate the VH data with different demographics. The results based on the first 990 cases will be available soon. Correlation between temporal changes in plaque composition and circulating biomarkers have been recently assessed in the Integrated Biomarker and Imaging Study (IBIS)1 sub-study where 20 non-culprit coronary plaques with no flow-limiting stenosis from patients referred for PCI were studied. After six months, an overall decrease in biomarker levels was not coupled with changes in IVUS-VH plaque size or composition, suggesting that the relationship between plaque burden, plaque composition and treatment is complex and needs to be further investigated. The IBIS2 study, a European multicentre randomised clinical study, uses palpography and VH alongside circulating biomarkers and endothelial function to estimate the effect of a new GSK Lp-PLA(2) inhibitor.

**Future Challenges in the Treatment of Vulnerable Plaques**

With the concept of ‘vulnerable’ plaque not nearly as straightforward as once thought, there are challenges to creating a local interventional approach for asymptomatic vulnerable plaques. First, there must be an ability to identify vulnerable plaque with non-invasive or invasive techniques. It has been demonstrated that coronary plaque composition can be predicted via VH-IVUS, allowing realtime analysis and in vivo plaque characterisation, but clear identification of TCFA is not yet possible and, moreover, the severity of the inflammatory infiltration of the cap, which certainly plays a major role in plaque disruption, can not be evaluated as yet.

A second challenge is that a lesion-specific local intervention requires that the number of vulnerable plaques in each patient needs to be known and the number of such lesions needs to be limited. That is not the case, however. Several pathological studies indicate the presence of multiple ‘lipid-rich’ vulnerable plaques in patients dying after ACS or with sudden coronary death. Furthermore, multiple complex plaques have been widely reported, in both culprit and non-culprit arteries, including up to 79% of patients referred for PCI after ACS. Further complicating the issue is the fact that coronary occlusion and MI usually evolve from mild to moderate stenosis – 68% of the time, according to different angiographic studies.

The third and fourth challenge to a lesion-specific, local interventional approach to vulnerable plaques is that the natural history of vulnerable plaque (with respect to incidence of acute events) has to be documented in patients treated with patient-specific systemic therapy; and the approach has to be proven to significantly reduce the incidence of future events relative to its natural history. At this time, neither is documented/proved.

Fifth, the authors believe that at the current stage it is not possible to know which vulnerable plaques will never rupture. Although it is suspected to be the vast majority of them, a more appropriate target for local therapy might have to be selected. In this setting, asymptomatic healed ruptured plaques might be more appropriate as these are the immediate precursors to AMI. In addition, targeting not only the vulnerable plaque but also the vulnerable blood (prone to thrombosis) and/or vulnerable myocardium (prone to life-threatening arrhythmia) may be also important to reduce the risk of fatal events.

**Conclusion**

Because we now recognise atherosclerosis as a diffuse, multisystem disease, it is essential to assess total patient vulnerability and not just search for a single, unstable coronary plaque. Future efforts may identify plaques that are on a trajectory of evolution towards a vulnerable state, and help target interventions to those plaques most likely to develop plaque disruption and related complications. Similarly, there may be a time when factors that protect plaques from becoming vulnerable will be identified. Until then, the authors go in search of the vulnerable patients in their practice who, with optimal systemic and local care, may end up with far fewer vulnerable plaques to worry about. By the means of imaging modalities like VH-IVUS we have just started this exciting journey, but ‘the way to Tipperary’ is still a long way to go.