This editorial refers to ‘Global characterization of coronary plaque rupture phenotype using three-vessel intravascular ultrasound radiofrequency data analysis’ by G.A. Rodriguez-Granillo et al., on page 1921

Imaging modalities that identify plaques vulnerable to rupture offer the possibility of preventing the most common substrate of coronary thrombosis. The incidence of progression of thin-cap atheroma, as identified at PCI, is largely unknown. Glaser et al. have demonstrated that at 1-year follow-up of a cohort of patients undergoing PCI, at least 6% develop progression of disease requiring additional PCI for another target lesion. The major predictors of plaque progression were multivessel disease, prior PCI, and age less than 65 years. Goldstein et al. demonstrated that 17% of acute MI patients with multiple complex angiographic lesions undergo PCI of non-culprit lesions within 1 year. These data underscore the need for identifying those plaques in high-risk patients who will benefit from prophylactic intervention. The hope is that newer imaging modalities, such as IVUS-virtual histology (VH) will precisely identify those lesions.

Rodriguez-Granillo et al. describe IVUS-VH in a prospective study of 40 patients referred for cardiac catheterization: there were 13 with stable angina, 12 with unstable angina, and 15 with acute myocardial infarction. The risk factor profiles were fairly typical of patients with coronary artery disease (CAD): 10% of patients had diabetes, 73% were male, 38% were smokers, and 50% had elevated cholesterol. Although three-vessel IVUS was the goal in all patients, only two-vessel characterization was possible in nine of the 40 patients. PR was identified in 26 patients and, as expected, was more frequent in patients with acute myocardial infarction and unstable angina. They concluded that patients with plaque ruptures have larger body mass index (BMI) when compared with those without plaque rupture and were more likely smokers and that patients with ruptures had more diffuse calcification and necrotic core area.

VH refers to spectral analysis of ultrasound backscatter radiofrequency signals. Refinements of IVUS to improve spatial resolution include 3D IVUS with integrated backscatter and wavelet analysis. Limitations of IVUS-VH include distinguishing necrotic core from calcification. Indeed, in the initial study of Nair et al., necrotic core and calcium were combined into a single colour (red for calcified necrosis). The degree of calcification in large cores is quite variable, ranging from microscopic calcification of macrophages to irregular blocks of calcium, often involving adjacent fibrous structures. This feature of necrotic core, namely variability in the degree and type of calcium deposition, often within a single lesion, renders interpretation of RF data difficult. Indeed, the image of plaque rupture rendered by VH in the manuscript of Rodriguez-Granillo et al. (Figure 1) is not typical of pathological sections of plaque rupture, as the lipid core is at an area of least plaque narrowing and the luminal thrombus cannot be ascertained.

Other imaging modalities offer alternate methodologies for the future of prophylactic coronary intervention. Non-invasive imaging, such as computed tomography, is overcoming motion artefacts by the use of multi-detector rows, ultra thin slices, and increased gantry speeds. Computed tomography has shown limited success in identifying thin-cap atheromas, using ex vivo histology of peripheral arteries, although using IVUS as the standard, there appears to be some promise with this method. Computed tomography is of limited use in calcified arteries, which is a significant drawback. Magnetic resonance imaging holds promise, as recent advances in hardware and pulse sequences have improved signal-to-noise ratio, allowing resolution of ≤400 μm. 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 catheter-based. In addition to IVUS, optical coherence tomography offers resolution as fine as 10 μm. 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 utilization of OCT as a diagnostic tool.

Despite ongoing limitations of plaque imaging, studies such as that of Rodriguez-Granillo et al. potentially usher a new era of in vivo plaque characterization. In the past, such studies were limited to autopsy series, and the current study begs comparison with autopsy data. Autopsy material predicates use of patients who either died from their disease or had incidental coronary disease and therefore may not be entirely representative of plaque findings in symptomatic patients who survive their disease. However, knowledge of fatal lesions is critical, as these are the patients one is especially interested in identifying.
prior to intervention. In our series or autopsy material, we have acquired data on thousands of coronary segments on hundreds of patients, most of who died suddenly with coronary disease, from one of several presumed mechanisms, including coronary thrombosis and ventricular instability secondary to chronic ischaemic lesions with or without ventricular hypertrophy. In these studies, we have made several observations that are of interest in comparison with data presented by Rodriguez-Granillo et al. Because the study of Rodriguez-Granillo et al. was limited to patients without significant calcification, it was somewhat biased to younger patients, with a mean age of 56 years. However, because sudden coronary death without prior history peaks at around 50 years, it is a good starting point for comparison with autopsy studies. Rodriguez-Granillo et al. found that the left anterior descending coronary artery was the most common site of PR, where it was usually proximal, in contrast to the right coronary artery (RCA), where it was as frequent as in the mid-artery. In a retrospective series of 79 ruptures, we have found that of 34 in the left anterior descending, 25 (74%) were in the proximal segment. In contrast, of 28 in the RCA, only 10 (36%) were in the proximal segment, 12 in the mid-artery, and six in the distal segment. Similarly, in the left circumflex, our autopsy findings mirror those of IVUS-VH in Rodriguez-Granillo et al.’s study, in that of 15 PR in the left circumflex, only four (27%) were in the proximal segment, the remainder in the mid-artery and obtuse marginal branches.

Further autopsy correlation of Rodriguez-Granillo et al.’s IVUS data entails the finding that the left anterior artery is most likely the representative of ‘unstable’ IVUS morphology, with large necrotic cores and high degrees of calcification, explaining higher restenosis rates in this vessel. The concept that calcification is inherently unstable, as suggested by Rodriguez-Granillo et al., is not necessarily valid, as the type of calcification, as determined by radiographic data, may be more important in plaque instability than the extent of calcification. The location of lipid cores in the study of Rodriguez-Granillo et al. was described only by vessel without indicating site (proximal, mid, or distal). This information may be of use to interventionists targeting vulnerable plaques. In a previous study by the same authors, IVUS-derived thin-cap atheromas were found predominantly proximal, with 35% in the first 10 mm, 31% from 11 to 20 mm, 19% from 21 to 30 mm, and 14% further distally.

As a correlation with autopsy findings, we have quantitated thin-cap fibroatheromas, a presumed measure of plaque ‘instability’, in the coronary trees of patients dying with severe coronary disease. Of a total of 131 lesions, the largest number (58) of thin-cap atheromas was present in the LAD, followed by the right coronary (32), left circumflex, marginal (30), and left main (11). We measured histomorphometrically the calcified area and necrotic core area and found them significantly higher in the LAD compared with other proximal vessels, as measured by total area as well as fractional area (unpublished data).

Although the relationship of BMI, elevated cholesterol, and smoking and the risk of coronary events is well established, Rodriguez-Granillo et al.’s study is among the first clinical imaging study to correlate plaque composition with risk factors. They demonstrate an increased prevalence of PR in patients with elevated BMI and smoking, among a group of patients with severe coronary disease. Interestingly, we have demonstrated a similar correlation between PR and smoking and BMI and between BMI and necrotic core area. Currently, IVUS-VH cannot distinguish TCFA from fibroatheromas on the basis of measurements of cap thickness, although IVUS-derived TCFA (IDTCCA) has been described as focal, necrotic core-rich plaques in contact with the lumen, and a percent atheroma volume >40%. In this study, no correlation was found with risk factors and IDTCCA, although there was an association with unstable coronary syndromes. In the future, as imaging detection of TCFA becomes more refined, the finding of a TCFA in one vessel should prompt the search for target lesions for potential intervention in other vessels. Refined coronary imaging techniques will eventually corroborate autopsy studies, which have demonstrated the heterogeneity of coronary atherosclerotic lesions as stratified by individual patient risk factor profile.

In Rodriguez-Granillo et al.’s study, PR was defined as ‘a ruptured capsule with an underlying cavity or plaque excavation by atheromatous extrusion with no visible capsule.’ Because of the varied histological appearances of disrupted plaques, from small cracks in the fibrous cap with minimal luminal thrombus to large rents with occlusive thrombi, it is tempting to question the accuracy of imaging in identifying all ruptured lesions accurately. However, ongoing comparisons of IVUS-VH data ex vivo and with autopsy material will provide corroborative evidence of the validity of imaging and, ultimately, information allowing for more specific intervention tailored to the heterogeneous nature of coronary atherosclerosis.

Conflict of interest: none declared.

References