Coronary computed tomography angiography (CTA) is an accurate non-invasive method for the detection of and especially ruling out obstructive coronary artery disease (CAD) in appropriately selected patients. After its arrival, it has become possible to evaluate both coronary anatomy and functional significance of stenosis non-invasively by combined or hybrid coronary CTA and myocardial perfusion imaging (MPI). Functionally significant CAD is currently the cornerstone for selection of further medical and invasive therapy, but the non-obstructive plaques are also common in patients referred for coronary CTA and might have significant implications for patients’ prognosis.

The majority of coronary thrombi and subsequent acute coronary syndromes (ACS) are caused by plaque rupture. Prototype of the rupture-prone plaque contains a large, lipid-rich necrotic core that is covered by a thin and inflamed fibrous cap, so-called thin-cap fibroatheroma (TCFA). The TCFA phenotype on radiofrequency intravascular ultrasound (IVUS virtual histology) imaging was associated with an increased risk of recurrent coronary events after an ACS in a prospective follow-up study. Of the events not related to the previous culprit lesion, most occurred at sites with TCFA, whereas the degree of stenosis was a poor predictor of plaque rupture as the average stenosis of culprit lesions at baseline was only 30%.

The extent and composition of non-obstructive atherosclerotic plaque on coronary CTA provide incremental information on patients’ prognosis over stenosis, traditional risk factors, and the results of MPI by identifying a patient group with intermediate risk of death or MI when compared with obstructive CAD. Simple characterization of plaque composition into non-calcified (lower density than the contrast-enhanced lumen), calcified (high density), and mixed (elements from both non-calcified and calcified) has been commonly adopted for clinical reporting. Some studies have shown prognostic value of the mixed and soft plaque phenotype as predictors of death and acute coronary events. In a recent study, a score including the number of proximal coronary segments with mixed or calcified plaques was the best CTA-based predictor of mortality. Given the complex morphology of high-risk plaques and the fact that probably only small fraction of non-obstructive lesions present such morphology, it is likely that risk stratification could be further improved with more specific markers.

Despite limited spatial resolution of coronary CTA for measuring the thickness of fibrous cap, TCFA are associated with some typical features in CTA images. Large plaque size, low CT attenuation of <30 HU, spotty calcification pattern, and positive vascular remodelling have been associated with culprit lesions of ACS. Motoyama et al. showed that a combination of low attenuation and positive remodelling was associated with >20% probability of an ACS within 2 years when compared with <1% in patients with neither of these. Napkin-ring-like sign or ring-like attenuation pattern is a recent surrogate marker of TCFA plaque morphology and predictor of ACS. This pattern corresponded to large lipid core (central low attenuation area) surrounded by outer fibrous plaque tissue (rim of high CT attenuation).

In this issue of EHJCI, Otsuka et al. report the relationship between three high-risk CT coronary plaque characteristics and ACS in 543 patients with non-obstructive atherosclerotic plaque. The patients were identified from 1956 mostly symptomatic individuals who underwent CTA for exclusion of CAD. Patients with high-grade stenosis were referred for invasive coronary angiography, whereas the haemodynamic significance of intermediate lesions was confirmed by MPI. Of note, despite normal perfusion, 30% of these plaques corresponded to 50–70% degree stenosis on CTA.

Coronary plaques were first classified as soft, calcified, or mixed. The soft plaques were further analysed for the presence of high-risk markers including positive remodelling, low attenuation (defined as <30 HU), and ring-like attenuation pattern. One-third (33%) of individuals had plaques with risk markers. Positive remodelling, low attenuation, or ring-like attenuation was present in 16, 12, and 3% of plaques, respectively. Two or three features were present in 4 and 1% of plaques, respectively.

The primary endpoint was ACS defined as cardiac death, non-fatal myocardial infarction (MI, n = 12), or unstable angina (UAP, n = 11) that required revascularization. During a median follow-up of 3.4 years, the average annual event rate was 1.2%. The presence of high-risk plaque features was a strong predictor of cardiac events (HR 9.4) with the annual rate of ACS being 3.2% in this group vs. 0.16% in the...
group without high-risk plaques. The high-risk features were present in 87% of the culprit lesions of ACS.

The findings of Otsuka provide additional evidence that CT-based markers of rupture-prone plaques can predict future ACS. An interesting feature of the study is that all patients had non-obstructive plaque as confirmed by normal MPI. In the absence of high-risk CTA features, the annual rate of ACS was very low compared with individuals with normal CTA.\(^{2,5,12}\)

The relatively straightforward approach to stratify plaques could identify a small subset of plaques associated with increased risk for ACS. The clinical utility of the classification remain to be tested in the future as it is obvious that measurement of any plaque characteristic depends on very high quality of CTA images. The inter-observer reproducibility of the high-risk signs is not clear especially among less experienced observers than the experts in the study of Otsuka et al.\(^{12}\)

Standardization of measurements is needed and probably automated software could help to achieve this.

A limitation of the study is the low number of events in this low-risk patient population and that half of the events were UAP the definition of which is sometimes difficult. More outcome data on these risk markers are needed, especially on their association with mortality. Future studies should also define relative strengths of high-risk plaque phenotype vs. other CT-based risk scores including coronary calcium and proximal location that is typical for high-risk plaques and predicted events in a recent study.\(^7\)

There is a need for more prospective outcome studies and intervention studies to define the clinical value of the promising methods for identifying high-risk plaques by CTA.

The ultimate proof of clinical usefulness of CT-based risk stratification would be that imaging-targeted interventions to stabilize plaque could be shown to improve outcomes.\(^3\)

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References