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Editorial

Do we really need another individual coronary plaque characterization measurement?

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Non-calcified coronary artery plaques with a large necrotic core covered by a thin fibrous cap are among the most vulnerable to rupture and precipitate an acute coronary syndrome (ACS) (Fig. 1A) [1,2]. These higher-risk "lipid-rich" plaques have lower attenuation values [measured in Hounsfield units (HU)] by coronary CT angiography (CCTA) than lower-risk "fibrous" plaques. However, HU values within individual plaques vary, resulting in significant overlap between lipid-rich and fibrous plaques [3]. Moreover, HU values are influenced by inherent, test-specific characteristics including adjacent intraluminal contrast concentration and image reconstruction techniques [4,5].

Given the difficulty in establishing a simple HU cut-off value for differentiating lipid-rich from fibrous plaques, Nakajima and colleagues, in this issue of *Atherosclerosis,* explored the clinical feasibility of using effective atomic number (EAN) values [6]. This novel tissue density-independent measurement was derived from single-source dual-energy CT, which recently has been shown to significantly reduce beam-hardening artifacts and improve image quality of CCTA [7,8]. In their study, Nakajima et al. included 11 patients who underwent single-source dual-energy CCTA and intravascular ultrasound (IVUS) imaging. Using established IVUS criteria, the authors classified 44 non-calcified coronary artery plaques as either fibrous (n = 13 plaques) or soft (n = 29 plaques) (Fig. 1B). The mean HU value and the mean EAN value for soft plaques were both significantly lower in soft plaques *versus* fibrous plaques. However, on receiver operating characteristic analysis for classifying soft *versus* fibrous plaque as defined by IVUS, the area under the curve for mean effective atomic number value was significantly greater (0.91; 95% confidence interval 0.73–0.97) than for mean HU value (0.79; 95% confidence interval 0.60–0.90; $p = 0.046$).

These findings from Nakajima et al. are novel in their suggestion that EAN values derived from single-source dual-energy CCTA may be a clinically useful alternative to HU values for differentiating soft and fibrous non-calcified plaques on CCTA. The fact that the authors were able to find a statistically significant difference in the receiver operating characteristic analysis for classification with such a small cohort suggests a strong signal. Furthermore, their data are remarkably similar to previously published findings that single-source dual-energy-derived EAN can help differentiate between soft and fibrous non-calcified carotid artery plaques [9]. Overall, the strength of these novel data warrant additional investigation in a larger patient population.

Given that single-source dual-energy CCTA is still limited in clinical use, it may be quite some time before such a follow-up study could be performed. Furthermore, EAN should be compared against newer automated plaque quantification software tools that have been shown to improve HU value measurement compared with manual analysis [10]. Comparing against a more accurate measurement of CT-derived HU values may attenuate the apparent advantage of EAN in differentiating soft and fibrous plaques. Moreover, comparison to data using intravascular ultrasound radiofrequency (IVUS-RF) analysis (Fig. 1C) [11,12] or newer approaches with ^{18}F-sodium fluoride uptake on positron emission tomography (PET) may also help identify high-risk coronary plaques (Fig. 1D) [13]. Future studies could also compare EAN (Fig. 1E) to a broad range of CCTA-identified 'high-risk' plaque features that have been associated with future ACS (i.e. 'napkin-ring' sign, spotty calcification, positive remodeling, and low attenuation plaque; Fig. 1F–I). Unfortunately, such features have limited positive predictive value for future ACS when compared to CCTA-derived luminal stenosis [14] or coronary plaque volume alone [15–17]. In this context, it is unclear whether EAN will significantly improve our ability to predict ACS beyond available plaque measures. To prove the independent and incremental value of EAN, future studies should focus on the requirements of a good prognostic test. Namely, outcomes-based validation and reliability studies are needed to prove new techniques can identify patients at low-risk for adverse events, define clear gradations of risk, and concentrate risk in patients with an abnormal test [18].

In summary, the findings of Nakajima et al. are novel and provocative. Their suggestion, that single-source dual-energy-derived effective atomic number values may better differentiate between soft and fibrous non-calcified plaques on CCTA than HU values, needs to be further validated in a larger cohort, in a study that ideally uses automated plaque quantification software for HU value measurement, includes comparison against the broad range of individual plaque measures already available, and establishes independent and incremental predictive value for relevant patient outcomes.

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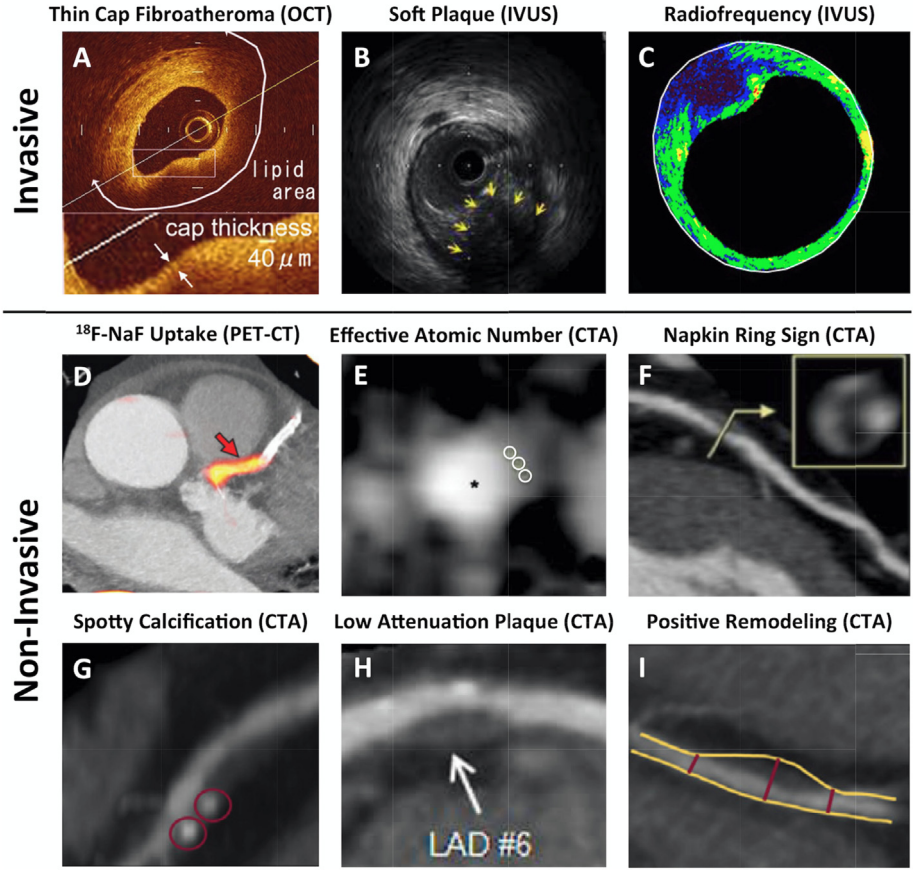

Fig. 1. Examples of plaque measures identified by invasive and non-invasive imaging.
(A) Optical coherence tomography (OCT) showing a thin-cap fibroatheroma (reproduced with permission [2]), (B) intravascular ultrasound (IVUS) identified soft plaque (yellow arrows; reproduced with permission [6]), (C) color-coded integrated backscatter IVUS images of a coronary artery plaque and overlying fibrous cap [fibrous (green), dense fibrosis (yellow), lipid pool (blue and purple), calcification (red); reproduced with permission [19]], (D) positron emission tomography computed tomogram (PET-CT)-identified ^{18}F-sodium fluoride (NaF) uptake at the site of a culprit plaque (red arrow; reproduced with permission [13]), (E) coronary computed tomography angiography (CCTA)-identified effective atomic number (EAN) (reproduced with permission [6]), (F) CCTA-identified 'napkin ring sign' (reproduced with permission [20]), (G) CCTA-identified spotty calcification (reproduced with permission [14]), (H) CCTA-identified low attenuation plaque (reproduced with permission [16]), (I) CCTA-identified positive remodeling (reproduced with permission [14]) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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