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EACVI POSITION PAPER

Contemporary rationale for non-invasive imaging of adverse coronary plaque features to identify the vulnerable patient: a Position Paper from the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology and the European Association of Cardiovascular Imaging

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Atherosclerotic plaques prone to rupture may cause acute myocardial infarction (MI) but can also heal without causing an event. Certain common histopathological features, including inflammation, a thin fibrous cap, positive remodelling, a large necrotic core, microcalcification, and plaque haemorrhage are commonly found in plaques causing an acute event. Recent advances in imaging techniques have made it possible to detect not only luminal stenosis and overall coronary atherosclerosis burden but also to identify such adverse plaque characteristics. However, the predictive value of identifying individual adverse atherosclerotic plaques for future events has remained poor. In this Position Paper, the relationship between vulnerable plaque imaging and MI is addressed, mainly for non-invasive assessments but also for invasive imaging of adverse plaques in patients undergoing invasive coronary angiography. Dynamic changes in atherosclerotic plaque development and composition may indicate that an adverse plaque phenotype should be considered at the patient level rather than for individual plaques. Imaging of adverse plaque burden throughout the coronary vascular tree, in combination with biomarkers and biomechanical parameters, therefore holds promise for identifying subjects at increased risk of MI and for guiding medical and invasive treatment.

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Introduction

Myocardial infarction (MI) is one of the leading causes of death globally, the majority of which are due to acute atherosclerotic plaque rupture. Identifying patients at risk of MI is highly challenging. The traditional imaging approach has been to look for obstructive coronary stenoses and whilst this remains important with respect to symptom assessment, percutaneous revascularization of obstructive stenosis has consistently failed to reduce the future incidence of MI.[1–3] This suggests the link between obstructive stenosis or myocardial ischaemia and MI is associative but not directly causative. Imaging assessments of plaque burden appear to offer better and more direct prediction of thrombotic events: the more plaques a patient has, the more likely a plaque will rupture and cause an MI.[4–6] However, risk prediction remains imperfect and computed tomography (CT) calcium scoring, perhaps the most common method of assessing plaque burden, increases and not decreases in response to preventative medication such as statins. Furthermore, it is critical to consider plaque phenotype and unstable forms of atherosclerotic plaque more likely to precipitate a thrombotic event.

Pathological observations more than 40 years ago revealed that culprit plaques responsible for acute MI have certain common histological characteristics.[7] These include inflammation, a thin fibrous cap, positive remodelling, a large necrotic core, microcalcification and plaque haemorrhage, often found together in the so-called thin-capped fibroatheroma.[8] Each of these adverse plaque characteristics is a potentially important imaging target, based upon the rationale that they may demarcate plaques that have an enhanced risk of rupture.[9] In contrast, stable plaques at relatively low risk of rupture have different characteristics including, absence of a necrotic core, large macroscopic deposits of calcium, and a thick fibrous cap. Non-invasive and invasive imaging technologies have advanced considerably over recent years and we now have techniques at our disposal that can reliably identify each of the adverse plaque features (*Figure 1*).

The main problem with this approach is the poor positive predictive value that these imaging-based plaque characteristics have demonstrated for clinical events. In the landmark PROSPECT trial, 596 thin cap fibroatheromas were identified using virtual histology intravascular ultrasound (VH-IVUS), but only six patients had an MI within 3.4 years.[10] In the recent SCOT-HEART trial, 1376 plaques with adverse characteristics (positive remodelling or plaques with low attenuation as a marker of necrotic core) were identified on CT, yet across the whole cohort, only 41 patients had an MI after 4.7 years.[4,11] Similarly, in the PROMISE trial, 1019 coronary plaques with adverse characteristics (positive remodelling, low CT attenuation, napkin-ring sign) were observed on CT, yet only 24 subsequent non-fatal MIs occurred.[12] The relatively low rates of MI in these studies may reflect selection bias in recruitment or recent advances in atherosclerosis therapy. Regardless, given that these studies have demonstrated that only a small minority of the plaques with adverse imaging characteristics go on to cause MI, observers have questioned[13] the very rationale for identifying them. On this background, we believe there is a clear and important need to re-evaluate the rationale for imaging plaque composition and to outline the exciting future that this field has and the pathway by which it might be used to improve patient assessment and outcomes. The aim of this Position Paper, co-authored by the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology and the European Association of Cardiovascular Imaging (EACVI) together with an assembled group of international participants from the field, is therefore to summarize the existing data on the relationship between vulnerable plaque imaging and MI, to discuss possible reasons for the low predictive value of imaging, and to address new approaches to improve its predictive value. This manuscript largely focuses on non-invasive assessments, although we will briefly describe the role that invasive imaging of adverse plaque might play in those patients undergoing invasive angiography. Importantly, this statement also focuses on *coronary* atherosclerosis and MI, which may not be equally applicable to cerebrovascular and other vascular beds where the pathophysiology and disease aetiology have important differences.

Terminology

The terms 'vulnerable plaque' and 'high-risk plaque' were proposed as synonyms for plaques at increased risk of thrombosis or rapid stenosis progression.[7,8] Although not intended, both terms might give the impression that these lesions are about to cause an imminent event. However, not all such plaques will rupture and not all rupture events cause MI. Thus, the terms vulnerable and high-risk plaque should be used with caution, indeed there is some debate as to whether new terminology is now required. Reference to adverse plaques (those plaques with the adverse plaque characteristics described above) is potentially attractive and is utilized interchangeably with the term vulnerable plaque in the remainder of the manuscript.

Explanation for the poor predictive value of adverse plaques identified on imaging

What is the explanation for why so few adverse plaques on imaging go on to cause an MI? It is possible that the imaging techniques so far developed are not adequate or we are not imaging the correct combination of features, however, there may be other more fundamental explanations. The initial pathological studies that introduced the concept of the vulnerable plaque were retrospective and did not provide

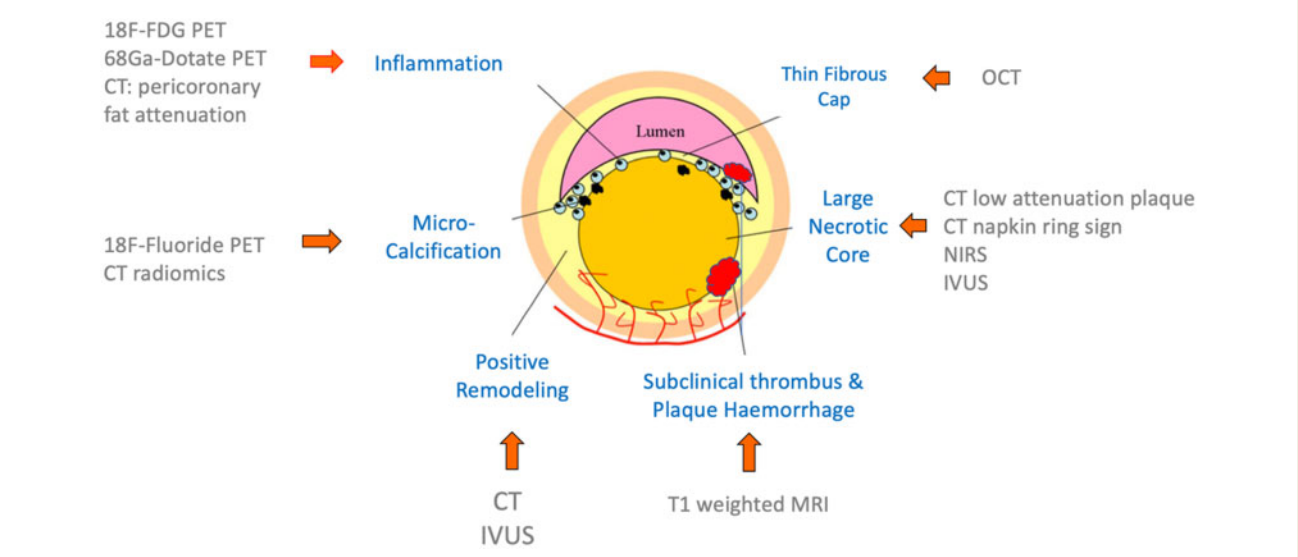

Figure 1 Features of the vulnerable plaque and imaging techniques to detect these features adapted from Vancraeynest *et al*.

us with information about the prevalence of vulnerable coronary plaques in the general population, their natural history or their haemodynamic or biomechanical environment. Moreover, they are now out-dated and the pathophysiology of atherosclerotic disease may have changed due to improved medical therapy and reductions in smoking, with a greater proportion of atherothrombotic events due to plaque erosion rather than rupture.[14]

Longitudinal imaging studies have recently demonstrated that plaques with at least one adverse feature are in fact relatively common and appear dynamic, with the ability to revert to a more stable phenotype spontaneously or in response to medications, such as statin therapy. Moreover, adverse plaques can develop at other sites in the coronary vasculature.[15] Vulnerable plaques can therefore develop, heal or indeed rupture, under the influence of multiple factors including haemodynamic stress.[16,17] Importantly, it would appear that only a minority rupture and that even if rupture occurs, this does not necessarily result in an MI: evidence of old healed plaque rupture occurs in more than four-fifths of lesions with >50% luminal stenosis.[18] Plaque rupture therefore frequently results in subclinical plaque growth rather than MI, dependent in part on the thrombogenicity of the blood.

With these important pathophysiological insights in mind, it is perhaps unsurprising that only a small proportion of the adverse plaques identified on coronary imaging go on themselves to rupture and to cause MI (*Figure 2*).

Adverse plaque imaging to identify vulnerable patients

Based upon these observations, the rationale for contemporary non-invasive adverse plaque imaging works better at the patient level. Patients with a tendency to developing vulnerable plaques will develop many such coronary plaques at different sites over time in a dynamic process of formation and healing. Whilst the specific plaque identified at the time of imaging may itself be unlikely to cause an MI, the patient remains at increased risk from one of the many other or future adverse plaques that will develop over time.

This concept is supported by an expanding literature of large multicentre imaging studies using different modalities to identify different adverse plaque characteristics over the whole coronary tree. In both the PROMISE and SCOT-HEART randomized controlled trials, patients with CT evidence of an adverse coronary plaque (defined by positive remodelling and low attenuation) demonstrated an increased future risk of MI.[4,12] The prognostic value of T_1-weighted magnetic resonance imaging, identifying plaques with intraplaque haemorrhage or luminal thrombosis, has also demonstrated this phenomenon with 41 of 159 patients identified with a high-intensity plaque going on to develop MI.[20] Interestingly, identification of similar high-intensity carotid plaque also predicts coronary events, highlighting the systemic nature of atherosclerosis.[21]

Future directions

Non-invasive imaging has exciting potential to improve clinical risk assessment using adverse plaque features to identify vulnerable patients with a higher likelihood of plaque rupture and clinical events. However, several steps remain before routine imaging of coronary plaque type can be recommended. First, we need to understand which imaging modality is best suited for the identification of adverse plaque features at the patient level. Important considerations include coverage, cost, ease of scanning, positive predictive value, and clinical availability. Of all the current non-invasive imaging modalities, CT would appear at the forefront given the breadth of supporting literature and its increasing use in patients with chronic coronary syndromes. However, one notable weakness of all methods for imaging adverse plaque has been their inability to improve upon the

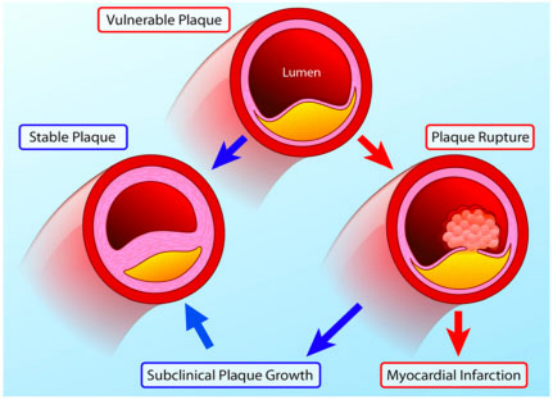

Figure 2 Dynamic nature and fate of vulnerable plaques. Image adapted from Dweck *et al.*[19]

prognostic power of much simpler assessments of plaque burden (e.g. CT calcium scoring).[4] Indeed, this lack of incremental prognostic information has made it hard to justify the added time involved in the evaluation of plaque type during routine practice.

How might the required advances be achieved? Assembling an overall risk profile by considering plaque type across the entire coronary tree, 'the adverse plaque burden', might further improve such risk prediction, with the notion that multiple plaques with multiple adverse plaque features carry a larger risk than identification of a single plaque. This is supported by a recent publication demonstrating that the low attenuation plaque burden (the burden of plaque <30 HU indicative of necrotic core) was the strongest predictor of future MI in patients with chest pain undergoing CTCA, outperforming cardiovascular risk factors, luminal stenosis severity, CT calcium scoring, and the total plaque burden.[22] Other approaches that quantify the burden of other adverse plaque characteristics, look at the position of adverse plaques within the coronary vasculature or seek to assess disease activity within the vasculature may also hold value.

There is interest in combining multiple different adverse plaque characteristics to improve predictive power. For instance, invasive imaging shows the predictive value for major adverse cardiovascular events (including revascularization) provided by the combination of plaque burden >70%, thin-capped fibroatheroma, and minimal lumen area <4 mm.[7,10] The recent CLIMA study demonstrated that patients with lesions in the left anterior descending artery that had four adverse plaque characteristics on optical coherence tomography had a seven-fold risk of subsequent MI or coronary death.[23] Similarly, many CT studies have shown that the simultaneous presence of multiple adverse CT features appears to improve risk prediction.[24,25] More research is needed that identifies the relative risk of each separate plaque feature and their composite for MI. The extension of this concept is to combine adverse plaque imaging with other cardiovascular risk factors, biomechanics and blood biomarkers to derive the most accurate risk stratification models.[26–28] In particular, combination with assessments of blood thrombogenicity, that is not captured with current imaging approaches, is of major importance. Other blood biomarkers may also improve risk stratification, whilst polygenetic risk scores may add important information related to the long-term risk of MI determined by heredity.

There are a large number of adverse plaque non-invasive imaging techniques and post-processing approaches in development that may improve prognostic power even further. These include 18F-fluoride positron emission tomography—a marker of calcification of disease activity in the coronary arteries (NCT02278211),[29,30] and CT assessments of perivascular fat attenuation—an indirect marker of coronary plaque inflammation.[31] Importantly, both approaches have recently demonstrated their ability to predict MI above and beyond the information provided by plaque burden.[31,32] Assessments of shear stress hold promise,[33] demonstrating incremental benefit to simple plaque characteristic assessments in the PROSPECT[34] and the FAME II trial.[27] Traditional physiological assessments of ischaemia and perfusion (e.g. stress echocardiography, myocardial perfusion imaging, fractional flow reserve) have provided prognostic information over many decades and are widely employed although further work is required to assess whether they provide incremental prognostic information beyond plaque burden assessments.[22] Quantitative plaque analysis may overcome the limited reproducibility of visual CT plaque characterization, whilst radiomics allows extraction of numerous quantitative plaque features from coronary CT angiography and in which spatial patterns are described by hundreds of variables instead of relying only on a handful.[35,36] Deep-learning techniques can create algorithms aimed at improving identification of adverse plaque features, based upon a non-constrained approach, linking plaque features associated with adverse outcome without explicit instructions as to which features may be important. Similar approaches have already shown their ability to improve detection of flow-limiting coronary artery lesions.[37] Finally, there may be value in applying adverse plaque imaging to specific patient groups, such as patients with non-obstructive coronary plaque disease. In the PROMISE and SCOT-HEART trials, 66% and 42% of MIs, respectively, occurred in patients with non-obstructive disease.[4,12] Patients with non-obstructive coronary artery disease are therefore an important group in whom further risk stratification to direct therapy may be warranted. Data from PROMISE suggest that adverse plaque imaging could be used to fulfil this role with the presence of adverse plaque nearly doubling the risk of MACE in patients with non-obstructive coronary artery disease.[12]

How might vulnerable plaque imaging guide future patient management?

It is worth considering how non-invasive imaging of adverse plaque features might impact upon patient care and management (*Figure 3*). Improved methods of risk stratification may play an important role in up titrating therapy and deciding which patients should be treated with novel yet expensive drugs such as PCSK9 inhibitors. These drugs could be targeted to high-risk patients with adverse plaque phenotypes similar to strategies already used in oncology to direct novel expensive treatments. However, the opposite approach of withholding expensive or invasive treatments for low-risk patients with stable plaque phenotypes may prove similarly valuable by enhancing cost-effectiveness.[38] This strategy makes use of the low annual event rates

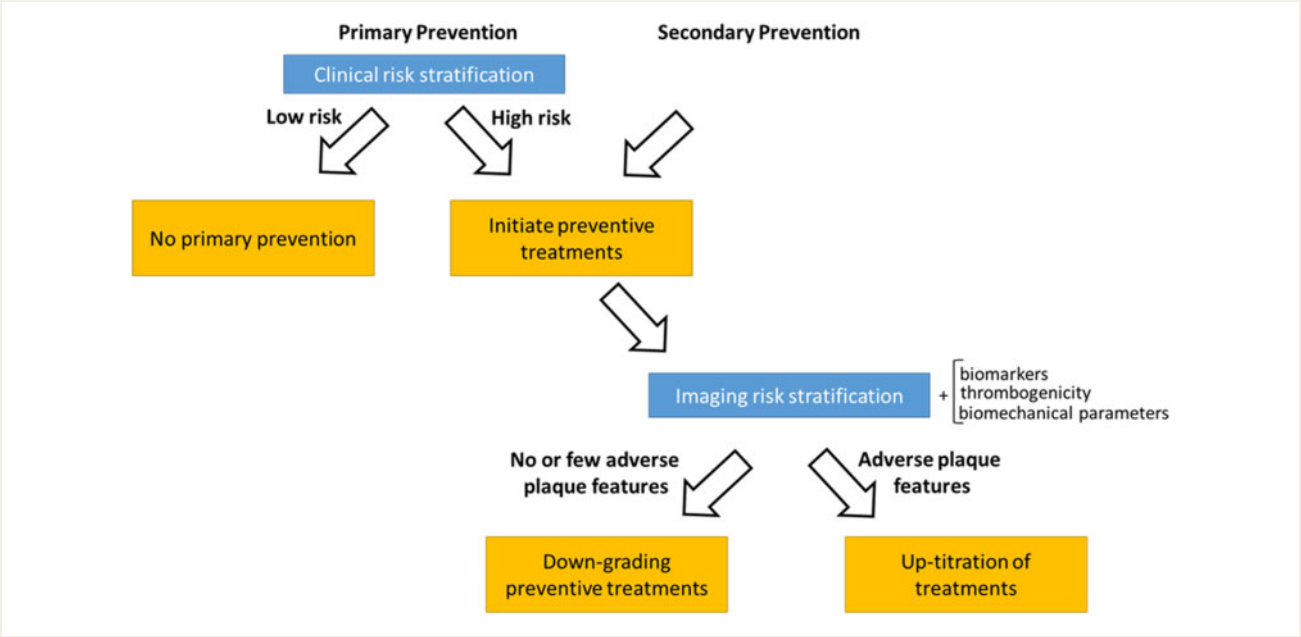

Figure 3 Illustration of how adverse plaque imaging might be used to both up titrate and down-grade therapeutic intervention.

observed in patients with stable patterns of atheroma and therefore takes advantage of the excellent negative predictive value that the absence of vulnerable plaque provides.[10] Perhaps patients with extensive disease but no adverse plaque features can be managed without the need for complex revascularization procedures or expensive novel medical therapies. Further observational data are now required to investigate these key issues, followed by rigorous randomized controlled trials investigating whether adverse plaque imaging can be used to direct the administration of different therapeutic strategies and improve patient care and outcomes. These should examine hard events such as fatal and non-fatal MI rather than biomarkers or 'soft' endpoints such as non-urgent revascularization; moreover, they should explore the cost-effectiveness of such a strategy.

Invasive adverse plaque imaging

Whilst the intrusive nature and current low predictive value of invasive adverse plaque imaging limits its role in the routine assessment of many patients with coronary artery disease, these approaches hold promise in guiding the management of patients already undergoing invasive angiography. For example, invasive plaque morphology assessments, using optical coherence tomography, intravascular ultrasound or near-infrared spectroscopy may help identify culprit plaques, or risk stratify non-culprit plaques in patients undergoing angiography following MI.[10,39,40] In patients with chronic coronary syndromes undergoing angiography, adverse plaque imaging may help guide revascularization in borderline lesions or identify patients at increased risk of periprocedural complications. It may also provide an indication of the adverse plaque burden and guide the intensity of medical therapy required. Similar to non-invasive imaging approaches, further data are required to demonstrate the value of such approaches, which have not yet demonstrated their efficacy and are not currently clinically indicated for this purpose.

Finally, it remains possible that invasive technology will identify individual plaque characteristics or combinations of different characteristics that allow for the precise detection of plaques that are at risk of imminent rupture. In this scenario, it can be envisioned that initial non-invasive imaging is followed by selective invasive imaging for improved risk prediction and treatment. This is an area of active research, which may yet reinvigorate the identification of individual vulnerable plaques and the rationale for interventional therapies directed at individual plaques. The PROSPECT 2 trial will further investigate the predictive value of invasive plaque assessments for future events (NCT02171065).

Conclusions

Imaging of adverse coronary plaque features has advanced greatly over the past decade and improved our understanding of the highly complex and dynamic nature of coronary atherosclerosis. Moreover, adverse non-invasive plaque imaging and assessment of the adverse coronary plaque burden is an exciting novel approach for identifying the vulnerable patient and improving patient risk stratification. Large multicentre observational studies and randomized controlled trials are now required to establish the optimal

adverse plaque imaging approach and the clinical utility of plaque phenotyping.

Positions

(1) In the coronary arteries, plaque composition is dynamic so that risk prediction based on identifying adverse plaque features currently works best at the level of the patient rather than for individual plaques.
(2) Non-invasive imaging of one or more adverse plaque features, preferably in combination with thrombogenicity, serum blood biomarkers, and biomechanical parameters, and establishing the adverse plaque burden across the coronary vasculature holds promise in identifying subjects at increased risk for MI (the vulnerable patient)
(3) For patient management, non-invasive adverse plaque imaging may be used to up titrate therapeutic intervention in patients at higher risk as well as down-grading treatment for patients at lower risk.
(4) Further studies and randomized controlled trials are required to establish the optimal adverse plaque imaging strategy and whether plaque phenotyping can be used to guide clinical decision-making and improve patient care.

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