Non-invasive vulnerable plaque imaging: how do we know that treatment works?

Anna Sannino†, Linda Brevetti†, Giuseppe Giugliano¹, Fernando Scudiero¹, Evelina Toscano¹, Ciro Mainolfi², Alberto Cuocolo², Cinzia Perrino¹, Eugenio Stabile¹, Bruno Trimarco¹, and Giovanni Esposito¹*

¹Cardiology and ²Nuclear Medicine, Department of Advanced Biomedical Sciences, University of Naples ‘Federico II’, Via Pansini, 5, 80131 Naples, Italy

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Atherosclerosis is an inflammatory disorder that can evolve into an acute clinical event by plaque development, rupture, and thrombosis. Plaque vulnerability represents the susceptibility of a plaque to rupture and to result in an acute cardiovascular event. Nevertheless, plaque vulnerability is not an established medical diagnosis, but rather an evolving concept that has gained attention to improve risk prediction. The availability of high-resolution imaging modalities has significantly facilitated the possibility of performing in vivo regression studies and documenting serial changes in plaque stability. This review summarizes the currently available non-invasive methods to identify vulnerable plaques and to evaluate the effects of the current cardiovascular treatments on plaque evolution.

Introduction

Atherosclerosis is a systemic, lipid-driven inflammatory disease of the arterial wall leading to multifocal plaque development. Despite great advances in cardiovascular medicine, atherosclerosis remains the foremost cause of death in developed industrialized countries and has become the leading cause of death globally.

While most plaques remain asymptomatic, some become obstructive and might cause symptoms because of impaired maximal blood flow. Alternatively, atherosclerosis may assume another pre-clinical form associated with potentially devastating effects: the development of often non-obstructive, but ‘unstable’ arterial plaques that may rupture and provoke acute thrombosis,1,2 causing acute myocardial infarction, stroke, or sudden death.3

It has been shown that vulnerable plaque is often less stenotic and, hence, is not detected as clinically significant stenosis with conventional methods.1,2,4 On the other hand, plaques with high-grade stenosis are not necessarily associated with major events such as stroke or myocardial infarction.1,2,4 Before major events happen, smaller plaque erosions with subsequent small thrombus layers may lead to less severe clinical findings, such as unstable angina without infarction or transient ischaemic attacks (TIAs).1,2,4,5 Thus, early detection of vulnerable plaque is of great clinical value because proper choice of prevention strategies may reduce the risk of major cardiovascular events.6

The archetypal presumed rupture-prone (vulnerable) plaque contains a large and soft lipid-rich necrotic core covered by a thin, inflamed fibrous cap1 infiltrated by macrophages and T cells.7 The release of cytokines and proteinases from these cells stimulates breakdown of cap collagen and smooth muscle cell apoptosis and thereby promotes plaque rupture.7 Thus, plaque inflammation and, in particular, the degree of macrophage infiltration are important predictors of plaque rupture and embolic events.8

Recently, the term ‘vulnerable patient’ has been introduced to indicate an individual with a high likelihood of experiencing a cardiac event, which is likely to have vulnerable blood (prone to thrombosis), vulnerable myocardium (prone to arrhythmia), and vulnerable plaque.9 In this regard, Naghavi et al.10 introduced the concept of a ‘vulnerability index’, which is a composite risk score that comprises the total burden of atherosclerosis and that indicates the likelihood that a patient with certain factors would have a clinical event in the coming year.

Plaque instability has been considered a multivessel phenomenon and, thus, vulnerable plaques may occur simultaneously in different parts of the arterial tree in the same individual. Indeed, it has been shown that patients with an acute coronary syndrome had...

* Corresponding author. Tel: +39 081 746 2240; Fax: +39 081 746 2240; Email: espogio@unina.it
† The first two authors equally contributed to this work.

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concomitantly multiple unstable plaques in the coronary tree and in the carotid district. Moreover, we recently demonstrated, in patients with lower extremities peripheral arterial disease (PAD), the association of unstable femoral plaques with increased risk of coronary and cerebrovascular events.

Several large clinical trials have demonstrated that one of the most important strategies to reduce cardiovascular events is the lipid-lowering therapy with statins, and this beneficial effect has been attributed partly to the ‘stabilization’ of vulnerable atheroma. On the contrary, little is known about the potential benefits of other important cardiovascular therapies such as beta-blockers or renin angiotensin system (RAS) inhibitors on plaque remodelling.

The aim of this review is to critically analyse the currently available non-invasive methods to identify vulnerable plaques and to evaluate the effects of current cardiovascular treatments on plaque evolution. Characterization of the possible diagnostic procedures necessary to identify the ‘vulnerable’ patient and to optimize his therapeutic management may become clinically very important to improve cardiovascular prognosis.

**Ultrasoundography**

High-resolution B-mode ultrasound is a simple, low-cost, and reliable non-invasive method for the evaluation of vascular stenosis and plaque echogenicity, which is known to be related to the histological characteristics of the atherosclerotic lesion. Examination of carotid arteries for intima-media thickness (IMT) is a widely used and reliable marker to reveal the severity of atherosclerosis and to predict the presence of coronary artery disease (CAD). Furthermore, assessment of carotid IMT has also been extensively shown to be a strong indicator for adverse cardiovascular events, and its regression with statin therapy may provide enhanced reduction in clinical coronary event rates. In addition, Reilly et al. first suspected that echo patterns in the B-mode image of a carotid plaque could be related to the composition of the plaque. Investigations of the relationship between cerebral symptoms and morphological characteristics of plaque defined by ultrasound found an association between clinical cerebral ischaemic events and ulceration, echolucency, intraplaque haemorrhage (IPH), and high lipid content. In particular, ulceration is believed to be important because it determines exposure of the thrombogenic layers of the plaque, with the possibility of subsequent thrombus formation.

Over the last decades, echogenicity has been differently defined and classified according to a variety of criteria. Since 1985, Johnson et al. distinguished plaques in calcified, dense, and soft. Subsequently, in 1988, Gray-Weale et al. described four plaque types, ranging from dominantly echoluent, to dominantly echogenic with small areas of echolucency, through two additional types of mixed echogenicity. Reilly et al. introduced characterization of plaque structure into homogeneous, having uniform high- or medium-level echoes, and heterogeneous, having high-, medium-, and low-level echoes, and containing areas with echogenicity similar to blood. Other groups used the criteria of the European Carotid Plaque Study Group since 1994: echo-rich, intermediate, and echoluent, combined with surface and structural characteristics. The echoluent plaques were associated with a high content of lipid and intraplaque haemorrhage, whereas echo-rich plaques contained more calcium and fibrous tissue. Ultrasound could not reliably distinguish between lipid and IPH, and this is why some studies have combined these two constituents in the term ‘soft tissue’. To summarize, plaques that appear hypoechoic on B-mode ultrasound have a pronounced inflammatory infiltration, a high lipid content, and are more prone to rupture, whereas hyperechoic plaques consist mainly of fibrous tissue, collagen, and calcium, which make them more stable.

To characterize B-mode images of plaques more objectively, digital image processing or videodensitometric analysis has been introduced. Using digital image processing, el-Barghouty et al. found that the content of soft tissue in the plaque was associated with a low gray-scale median (GSM) value of the plaque. Conversely, a high fibrous tissue content was associated with a high GSM value. This ultrasonographic index of echogenicity has emerged as an assessment methodology of carotid plaque vulnerability, and may help in the vascular risk stratification in order to target individuals at increased vascular risk for intensive preventive therapies and to monitor the effects of anti-atherosclerotic therapies. Interestingly, many studies have considered whether the lipid-lowering therapy with statins modifies the echogenicity of atherosclerotic plaques. Della-Morte et al. showed that carotid plaque echogenicity measured by ultrasonographic gray-scale densitometry decreased after short-term treatment with atorvastatin. In addition, an intensive

**Figure 1:** Example of hypo-anechoic carotid plaque (arrow) at B-mode (A) and duplex (B) ultrasonography. Such low echogenicity at B-mode ultrasound (plaque type 1, GSM 6.2) is suggestive of high lipid content, intraplaque haemorrhage, and pronounced inflammatory infiltration. Duplex ultrasound allows to better outline the plaque.
long-term atorvastatin therapy increased a GSM score, without regression of plaque size, in patients with carotid stenosis. An increasing echogenicity of vulnerable plaque in carotid districts, assessed by integrated back scatter, is present also in hypercholesterolemic and non-hypercholesterolemic patients with CAD after a short-term statin therapy.

A potential beneficial effect of β-blockers on plaque stability, assessed by GSM in carotid plaques, has been demonstrated by Ostling et al. After 36 months of treatment, plaques were more echogenic in participants treated with metoprolol CR/XL and fluvastatin (40 mg once daily) than in those treated with fluvastatin only.

Although this review focuses on the non-invasive imaging of the vulnerable plaque, it is worth mentioning that atherosclerotic plaques unapproachable by non-invasive ultrasonography, such as coronary plaques, can efficiently be assessed by alternative methods, such as invasive intravascular ultrasound (IVUS) or optical coherence tomography (OCT). IVUS uses an ultrasound transducer on the tip of a catheter to produce images for the evaluation of plaque size, distribution and composition, of vascular remodeling and vessel wall distensibility. IVUS is also used as a potential application for the identification of atheromas at risk of rupture. In contrast, OCT is an optical analogue of ultrasound imaging, recently proposed as a high-resolution imaging method for plaque characterization. In this regard, it has been shown that OCT reflects the macrophage content of the fibrous cap. All fibrous plaques, calcifications, and echolucent regions identified by IVUS are seen in OCT images. Moreover, compared with IVUS, OCT images provide additional morphological information, which could be used to improve plaque characterization.

Contrast-enhanced ultrasonography

Contrast ultrasound relies on the selective retention of the contrast agent at specific sites of disease. Different types of targeted contrast agents have been reported, most of which share in common the presence of a gas encapsulated by a shell of varying chemical formulation. Targeted micro-bubbles have undergone experimental evaluation to visualize cell surface structures or other features implicated in plaque rupture, such as neovascularization. A simple approach for targeting has been to take advantage of the natural ability of certain microbubble shell constituents to bind directly or indirectly to cells that have undergone pathological activation. A more specific approach has been to attach disease-targeted ligands, such as antibodies, small peptides, and glycoproteins, to the surface of ultrasound contrast agents. Accordingly, endothelial cell adhesion molecules, such as intracellular adhesion molecule-1, vascular cell adhesion molecule-1 (VCAM-1), and P-selectin, that play a critical role in the progression of atherosclerosis, are a popular target for micro-bubbles. Imaging of VCAM-1 and P-selectin has been used to detect the earliest stages of atherosclerotic disease even before the development of fatty streaks, supporting the notion that molecular imaging could be used to guide the use of the next generation of preventive therapies. Unfortunately, a limitation of molecular ultrasound imaging is that, first, only intravascular events can be accessed; then, a critical threshold amount of molecular expression may be needed to see attachment. Nevertheless, contrast ultrasound provides a good balance between spatial resolution and sensitivity to detect contrast agent, and these features make this technique well positioned among non-invasive methods in the assessment of the vulnerable plaque.

Immunoscintigraphy

Immunoscintigraphy is a non-invasive alternative technique based on the administration of radioactive tracers that localize into vulnerable plaque and the subsequent scan for radioactive emissions. Many radionuclide-labelled molecules have been proposed to investigate atherosclerotic plaques, such as low-density lipoproteins, haematoporphyrin derivatives, fibronectin, immunoglobulins, and platelets. Other investigations focused on antifibrin antibodies directed against D-dimers of cross-linked fibrin. The presence of insoluble fibrin represents an accurate marker of the activation of the coagulation cascade in the vessel lumen, potentially offering also the opportunity of an enhanced imaging, due to the lower background activity even in the absence of thrombi, as it is known that layers of insoluble fibrin are present inside uncomplicated atherosclerotic plaques.

Positron emission tomography

Positron emission tomography (PET) with F-18-fluorodeoxyglucose (FDG) is a molecular imaging technique that is highly sensitive to metabolically active processes using glucose as a fuel. FDG is a glucose analogue that is taken up by cells in proportion to their metabolic activity. Recently, arterial FDG-PET imaging has been extended to the study of the pathogenic mechanisms of atherosclerosis. FDG could be considered a marker of inflammation since macrophages, key inflammatory cells in plaque, have higher glucose metabolism than both surrounding plaque cells and healthy artery walls. Tawakol et al. showed that, in a rabbit model of atherosclerosis, there is a strong correlation between macrophage density and FDG uptake, and reported similar findings in patients with carotid artery disease, supporting the hypothesis that a higher FDG uptake identifies a more vulnerable plaque. Some studies have shown visualization of FDG uptake in coronary artery plaques. However, several technical issues limit its application: FDG uptake in adjacent structures such as the myocardium, cardiac motion during PET acquisition, and partial volume effect due to small coronary artery and the size of plaques. Furthermore, arterial FDG uptake positively correlates with levels of several circulating inflammatory biomarkers and molecular gene up-regulation of enzymes known to degrade the cellular matrix of vulnerable plaque, such as the matrix metalloproteinase (MMP) family, whose activity has been associated with advanced atherosclerosis and plaque rupture.

In the first prospective study using FDG-PET to quantify inflammation in atherosclerosis, Rudd et al. measured increased carotid artery FDG uptake in symptomatic lesions of patients with recent TIA. Furthermore, it has been shown that inflammatory activity of plaques can be assessed by FDG-PET not only in carotid and other brain supplying arteries, but also in the aorta, iliac, femoral, and coronary arteries. The different distributions of FDG uptake may reflect the different stages of atherosclerosis progression: a higher...
FDG uptake reveals concurrent extensive and advanced atherosclerosis. In fact, there is a significant correlation between FDG uptake and cardiovascular risk factors such as hypertension, smoking, hyperlipidaemia, being overweight, Type II diabetes, and a family history of CAD. Thus, higher FDG uptake might contribute to the identification of a subgroup of patients at high risk for cardiovascular events.

A recent study has shown that FDG uptake in atherosclerotic plaques is predictive of the future occurrence of cardiovascular events in neoplastic patients. Indeed, FDG-PET could be used not only to predict the risk of future plaque rupture and to identify a subset of high-risk patients who need of intensified medical therapy or carotid surgery to prevent stroke, but also to monitor the effectiveness of the reduction of vascular inflammation in response to lifestyle intervention on cardiovascular risk factors or to pharmacological treatments. Indeed, it has been demonstrated both in a rabbit model and in human patients that statin therapy is able to reduce FDG uptake. In conclusion, the identification of FDG uptake in vascular plaques may have important clinical implications to predict and prevent future cardiovascular events.

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) is a safe and non-invasive technique that, operating without X-rays, can be used to evaluate atherosclerosis or to guide therapy, since it possesses the superb spatial resolution necessary to image small-scale pathological findings such as atherosclerotic disease progression. However, it is a relatively signal-insensitive technique when compared with computed tomography (CT) or PET, requiring long scanning times to improve spatial resolution and to overcome its low temporal resolution.

As far as atherosclerotic lesions regard, MRI is able to characterize soft tissue components of plaque. It can identify, with high accuracy, sensitivity, and specificity, the lipid core and thin and/or ruptured, unstable, caps, which are strongly associated with having had a recent TIA or stroke. Moreover, MRI has emerged as a reliable and highly accurate tool to detect IPH in vivo, which highly correlates with plaque instability.

Target-specific contrast agents have recently been developed in order to better discriminate plaque components and then to overcome some MRI limitations, such as long time data acquisition. So far, molecular agents targeted to adhesion molecules, or high-density lipoprotein, MMPs, and macrophage scavenger receptors have been tested at the preclinical level, and agents targeted to fibrin and macrophages have already been used in patients.

One of the earliest applications of nanotechnology in MRI involved the use of paramagnetic iron oxide particles. Ruehm et al. demonstrated spontaneous phagocytic uptake of superparamagnetic iron oxide and ultra superparamagnetic iron oxide particles by macrophages in atherosclerotic plaque in hyperlipidaemic rabbits. In 2003, this finding was extended to human plaque (Figure 2). Recently, with the advent of fibrin-binding molecular MRI contrast agents and advances in coronary MRI techniques, it has become possible to obtain a direct imaging of coronary thrombosis.

Furthermore, MRI has been used to assess the efficacy of antiangiogenic strategies on the stabilization of aortic atherosclerotic plaques. Since IPH is considered a potential contributor to plaque destabilization, drugs acting specifically on neangiogenic growth might reduce plaque vulnerability. Winter et al. demonstrated the acute antiangiogenic effects of fumagillin, an antagonist of αvβ3 integrin, which is an adhesion molecule that promotes the formation of new blood vessels. In this study, the effect of αvβ3-targeted fumagillin nanoparticles was prolonged when combined with the use of atorvastatin, thus representing a potential anti-angiogenic and plaque stabilization strategy. Moreover, Moulton et al. showed that the inhibition of neovascularization by angiostatin reduced macrophage accumulation and plaque progression in mice. Subsequently, non-invasive vulnerable plaque imaging.
Corti et al.\textsuperscript{88} have prospectively shown that in patients with carotid or aortic plaques treated with statins for at least 1 year, the earliest appreciable change was a regression in plaque size. Longer follow-up indicated that regression of atherosclerotic lesions continues for at least 24 months, and that progressive remodelling of the arterial wall produces a significant increase in luminal area.\textsuperscript{89} These data have also been confirmed by Zhao et al.\textsuperscript{90} demonstrating how intensive lipid-lowering therapy significantly depletes carotid plaque lipid after 1 year of treatment, and continues in the second year. Subsequently, West et al.\textsuperscript{91} have studied the effects of lowering lipid strategies, with simvastatin 40 mg alone or simvastatin 40 mg plus ezetimibe 10 mg, on the regression of atherosclerotic lesions measured by MRI in the superficial femoral artery in patients affected by PAD. This study demonstrated that statin initiation with or without ezetimibe in statin-naive patients halts progression of peripheral atherosclerosis whereas, when ezetimibe is added to patients previously on statins, peripheral atherosclerosis progressed.\textsuperscript{91}

**Computed tomography**

Recent technological advances led to a growing interest in CT as a tool for the non-invasive characterization of atherosclerotic disease. When compared with MRI, CT is more signal-efficient and is able to provide high-spatial resolution images of the entire coronary arterial tree in a short period of sustained respiration, thereby reducing scanning time. By virtue of its ability to measure local tissue attenuation, multidetector (MD) CT also allows imaging of the vessel wall, potentially providing insights into the characteristics and extent of intramural atherosclerosis.\textsuperscript{92} MDCT can also help detecting some of the features associated with plaque vulnerability, such as more positive remodelling, the presence of spotty calcifications, and a lower plaque density (< 30 Hounsfield units).\textsuperscript{93} Figure 3 shows an example of contrast-enhanced CT angiography detection of plaques of different grade.

In the context of molecular imaging of intraplaque inflammation, CT has shown promising preliminary results in animal models, using targeted nanoparticle contrast agents, but the feasibility and clinical applicability of CT for molecular imaging of plaque vulnerability still awaits clinical translation to humans.\textsuperscript{94}

Monitoring atheroma progression using serial CT has been used to characterize the natural history of atherosclerosis and the effect of anti-atherosclerotic therapies. Uehara et al.\textsuperscript{95} quantitated the effect of 10 mg atorvastatin on the size and content of non-calcified coronary plaques (NCPs) using MDCT and by comparison of LDL cholesterol levels. In this study, atorvastatin decreased NCP area if LDL cholesterol levels were sufficiently reduced, in agreement with the result of studies using IVUS.

Soeda et al.\textsuperscript{96} demonstrated that rosuvastatin therapy (2.5–10 mg for 24 weeks) was able to reduce the volume of lipid cores in lipid-rich coronary plaques, and increased their CT attenuation value, reporting that dual-source CT is an effective modality for the non-invasive evaluation of high-risk coronary plaques in patients with acute

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**Figure 3:** Example of plaque detection by contrast-enhanced CT angiography. Some calcified plaques can be seen in the axial views of the suprarenal (upper left panel) and sub-renal (lower left panel) abdominal aorta. Multiple calcified plaques can be seen on multiplanar reformating coronal CT (right panel) in the abdominal aorta and iliac arteries.
coronary syndromes. Furthermore, using MDCT, Suzuki et al. demonstrated that the combination therapy of an RAS inhibitor with statin is more effective than statin alone in inhibiting atherosclerotic progression of coronary arteries and the aorta in patients with CAD.

**Future perspectives: hybrid techniques**

Several imaging platforms are currently available for targeted vascular imaging to acquire information on both anatomy and pathophysiology in the same imaging session using hybrid technology, such as PET/CT or PET/MRI. Indeed, PET imaging has relatively low spatial resolution, mandating the use of concurrent structural imaging (CT or MRI) to guide localization of the FDG signal, revealing whether the plaque is actually metabolically active or not.

Hybrid PET/CT enables measurement of functional and structural features of atherosclerosis, in which FDG uptake detects plaques with an ongoing inflammatory process, whereas CT identifies chronic calcification as a manifestation of the late stage of the disease. Examples of plaque detection by hybrid PET/CT are depicted in Figures 4 and 5.

FDG-PET/CT has also been used to detect the anti-inflammatory effect of short-term statin treatment on aortic lesions, in correlation with the circulating inflammatory biomarkers. In particular, a significant reduction of FDG activity was reached after atorvastatin treatment. These findings provide in vivo evidence that the medium dose of atorvastatin (40 mg) might have a beneficial effect on plaque stability in 12 weeks, suggesting that a relatively low dose and a short treatment interval are sufficient to observe changes in plaque burden. Ishii et al. prospectively assessed the effect of 6-month therapy with 5 vs. 20 mg of atorvastatin on reducing FDG uptake in aortic plaques with PET/CT, and showed that only

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**Figure 4:** Example of plaque detection by hybrid PET/CT. Contrast-enhanced middle-chest axial CT view shows parietal thin abnormality (thrombosis) of the ascending and descending aorta (A). Hybrid PET/CT scan demonstrates areas of inhomogeneous parietal FDG uptake in the thoracic aorta (arrows), suggesting an ongoing inflammatory process (B).

**Figure 5:** Example of plaque detection by hybrid PET/CT. Contrast-enhanced head, neck, and chest coronal multiplanar reformatting CT scan shows parietal thin abnormality of both carotid arteries and the aortic arch (A); PET (B) and hybrid PET/CT (C) scans show areas of increased FDG uptake in carotid arteries and aortic arch (arrows).
atovastatin 20 mg significantly reduced plaque inflammation. An example of evaluation by hybrid PET/CT of regression of plaque inflammation is depicted in Figure 6.

Emerging hybrid PET/MRI has considerable potential for cardiovascular imaging. In a recent study, the relationship between inflammation in PET and morphological features of carotid plaques associated with high risk of clinical events, such as lipid deposition, remodeling, and luminal irregularities, was studied in patients with PET and MRI co-registration. Carotid inflammation increased with the number of high-risk morphological features observed, supporting the concept that plaque inflammation and composition are closely linked. In the future, with new hardware developments and the introduction of combined PET and MRI scanners, it would be possible to add the most attractive aspects of both modalities in order to have a more profound look into the biology of atherosclerotic plaques.

Conclusions and clinical implications

Atherosclerosis involves undetected vascular changes, like calcifications or inflammatory infiltration of the vessels. The identification of preclinical atherosclerotic lesions allows the application of appropriate strategies to prevent its progression and promote its regression. Epidemiological studies have shown that major adverse cardiovascular events result from vulnerable plaque rupture, 1,2,7,10,104 confirming that biological composition and inflammatory state of an atherosclerotic plaque, rather than its degree of stenosis or size, may be the major determinants for acute clinical events. Thus, the opportunity to non-invasively and prospectively monitor vulnerable plaques, before their disruption and clinical expression, is a laudable and useful goal.

The above-mentioned non-invasive strategies may help to assess the effectiveness of therapy and to frame a subset of high-risk patients exposed to a more severe cardiovascular prognosis. However, there is currently no evidence supporting different therapeutic strategies in patients with and without vulnerable plaques. Therefore, the presence of calcified plaques cannot justify a milder treatment. Actually, optimal management of unstable plaques remains to be defined and tested prospectively, since it is unclear if invasive ‘cool down’ of inflamed atherosclerotic lesions has a favourable risk–benefit ratio. The identification of vulnerable plaques may, probably, suggest to the physician to have a ‘special attention’ towards these potentially higher cardiovascular risk patients. Thus, the appropriate use of any plaque imaging modality and consecutive interventions needs to be investigated in prospective clinical trials, ultimately leading to guidelines for identification, risk stratification, and therapy of patients with unstable plaques.

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References

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