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REVIEW ARTICLE

# Is regression of atherosclerotic plaque possible?☆

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Lipid-lowering therapy

**Abstract** As it is well-known, a thrombus evolving into a disrupted/eroded atherosclerotic plaque causes most acute coronary syndromes. Plaque stabilisation via reduction of the lipid core and/or thickening of the fibrous cap is one of the possible mechanisms accounted for the clinical benefits displayed by different anti-atherosclerotic strategies. The concept of plaque stabilisation was developed to explain how lipid-lowering agents could decrease adverse coronary events without substantial modifications of the atherosclerotic lesion ('angiographic paradox'). A number of imaging modalities (vascular ultrasound and virtual histology, MRI, optical coherence tomography, positron tomography, etc.) are used for non-invasive assessment of atherosclerosis; most of them can identify plaque volume and composition beyond lumen stenosis. An 'aggressive' lipid-lowering strategy is able to reduce the plaque burden and the incidence of cardiovascular events; this may be attributable, at least in part, to plaque-stabilising effects.


**PALABRAS CLAVE**
Aterosclerosis;
Estabilización de la placa;
Técnicas no invasivas de imagen vascular;
Hipolipemiantes

**¿Es posible la regresión de la placa aterosclerótica?**

**Resumen** La patogenia de los síndromes coronarios agudos está relacionada con la rotura o erosión de una placa aterosclerótica vulnerable. La estabilización de dicha placa, por reducción del núcleo lipídico y/o aumento de la capa fibrosa, sería uno de los mecanismos potencialmente beneficiosos observados con agentes antiateroscleróticos. El concepto de estabilización de la placa de ateroma se desarrolló para explicar el efecto beneficioso del tratamiento hipolipemiante, sin cambios apreciables en el tamaño y la morfología de la lesión aterosclerótica («paradoja angiográfica»). En la actualidad, el desarrollo de nuevas técnicas de imagen

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no invasivas (ultrasonido vascular e histología virtual, resonancia magnética, tomografía de coherencia óptica, etc.) permite determinar el volumen, el tamaño y la composición de la placa, con lo que es posible caracterizar las placas más vulnerables y, por consiguiente, más susceptibles de rotura. Una estrategia hipolipemiante «agresiva» puede estabilizar e incluso reducir de forma significativa la carga aterosclerótica y la incidencia de episodios vasculares, al menos en parte, a través de un efecto estabilizador de la placa.


## Introduction

The pathogenesis of acute cardiovascular syndromes is related to the breakage or erosion of a vulnerable atherosclerotic plaque.[1] Stabilising that plaque, by reducing the lipid core and/or increasing the fibrous cap, would be one of the potentially beneficial mechanisms observed with anti-atherosclerosis agents.[2] The concept of stabilising atheroma plaque was developed to explain the beneficial effect of lipid-lowering treatment with no appreciable changes in the size and morphology of the atherosclerotic lesion using angiography (''angiographic paradox'').

At present, the development of new non-invasive imaging techniques (intravascular ultrasonography [IVUS] + virtual histology, optical coherence tomography [OCT], magnetic resonance imaging, positron emission tomography [PET], etc.) enable atheroma plaques in the vascular tree to be identified early, as well as their volume, size, and composition. Therefore it is possible to characterise the most vulnerable plaques and, as a result, those most susceptible to breaking and thrombosis.[3] Stabilising vulnerable plaques, by reducing the lipid core and/or increasing the fibrous cap, would be one of the potentially important clinical benefits observed with some anti-atherosclerotic agents, primarily statins.

## Identifying high risk/vulnerable plaques

Plaque composition, more than the degree of stenosis, is the critical determining factor for the risk of breaking and subsequent thrombogenicity. Specifically, the necrotic core, fibrous cap, and inflammation are the main factors playing a role in plaque vulnerability. Of these, a thin fibrous cap (<54 $\mu$m), abundant necrotic core, and the degree of inflammatory infiltrate are considered to be the best discriminating factors of vulnerability.[4] Advances in understanding the cellular and molecular bases of plaque progression have enabled the physiopathological role of inflammation in vulnerable plaques to be established.[5] At present, it is known that inflammatory mediators associated with leucocyte activation promote progression; a clear example is interleukin 6 (IL-6), a cytokine associated with increased production of C-Reactive Protein, which is an established marker of cardiovascular risk.[6,7]

Better understanding the physiopathology of atherosclerosis and the development of new imaging techniques has enabled high-risk plaques to be better characterised.[8]

Coronary angiography has traditionally been the imaging test that best determines the degree of stenosis and it continues to be the technique used to guide revascularisation procedures, both surgical and intravascular catheterisation. Angiography provides information about the number and size of vascular stenoses; however, a low correlation has been observed between angiographic findings and risk factor modification, and moreover, it does not tell us anything about the plaque's composition.

Intravascular ultrasonography (IVUS) plus virtual histology enable atheroma plaques in the vascular tree to be identified, and can quantify the size, volume, composition, and distribution of the plaque. Similarly, IVUS can detect lesions in vessels without stenosis in the angiographic test and precisely identify areas with positive and negative remodelling, as well as the atherosclerotic ''burden''.[9]

Optical coherence tomography (OCT) enables several variables related to plaque morphology and composition to be detected, as well as the presence of calcium deposits, which are correlated with the extent of the atherosclerosis, although there is some controversy regarding the correlation between calcification and vulnerability.[9]

Magnetic resonance imaging possesses advantages over other imaging techniques, by not requiring the use of intravascular ionic contrasts. It also enables images to be obtained on several planes and provides information about vascular tissue composition. Recent research has demonstrated that it is possible to obtain images of not only the vascular lumen, but also the composition of the artery wall.[10]

Carotid ultrasonography detects the presence of focal atherosclerotic plaques and quantifies the carotid intima-media thickness (IMT). This is a non-invasive procedure that is standardised and has been validated in several studies. IMT, preferably measured in the common carotid artery, has been correlated with cardio- and cerebrovascular risk in different risk groups.[11]

## Measuring plaque response to systemic therapy

Statins have changed the natural history of atherosclerotic disease in general and coronary and cerebrovascular