

## Intravascular ultrasonography in coronary atherosclerosis trials

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**TO THE EDITOR:** In the article by Drs. Schoenhagen and Nissen (*Cleve Clin J Med* 2005; 72:487–496), the notion is proposed that a precise description of early coronary plaque progression could amount to a simplified marker of cardiac events.

Obviously, although no demonstration of clinical value in such a strategy can be offered as yet, the scientific and industry communities have been thrilled by this potentially innovative approach.

A main question to be asked in this regard seems to be: Is atherosclerotic heart disease a systemic, diffuse, continuously progressive process or a discontinuous and pulsatile process in location and time?

The overwhelming evidence from many years of practice in the coronary angiography era suggests that atherosclerotic heart disease is a diffuse, obligatory aging process (prominently influenced by lipid metabolism) only to a mild (though undeniable) degree. Both angina, which correlates mainly with the occurrence of localized subtotal obstructions, and acute myocardial infarction, which correlates with clot complications of ulcerated plaques, typically occur at the onset of discontinuous endoluminal accidents.

If studies using intravascular ultrasonography (IVUS) of the kind the authors mention at a pilot stage should be used only to confirm the role of lipids in predisposing patients to atherosclerotic heart disease, the cost-effectiveness of the project would be quite limited, though not irrelevant. Especially important, though not definitive, is the proof of regression as a response to intervention. However, it is the stage immediately preceding plaque rupture that should be serially and prospectively studied by IVUS in a large series of patients in longer-term studies, in order to better understand the critical changes that lead to the sudden clinical progression.

Additionally, systematic, serial IVUS studies could provide more sound interpretations of such basic phenomena as the mentioned positive vessel remodeling that occurs with aging: Is it really a consequence of initial atherosclerosis itself, as hypothesized by Glagov, or of pressure wear, as in aneurysm progression, or is it mainly (or also) a consequence of plaque outgrowth that occurs at the same time as lipid deposit?

In conclusion, IVUS studies could indeed offer great mechanistic information on different aspects of vascular diseases, but issues of methods and techniques demand careful attention, patience, and discipline.


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**IN REPLY:** Dr. Angelini emphasizes an intriguing observation about coronary artery disease. On the one hand, basic science has established the diffuse, systemic nature of atherosclerotic changes in the vessel wall beginning in early adulthood.<sup>1</sup> On the other hand, clinical syndromes of coronary artery disease and associated angiographic findings typically occur later in life and have a focal character.

Atherosclerosis imaging with tomographic modalities has reconciled these findings. As Dr. Angelini describes, arterial remodeling and plaque vulnerability are fundamental concepts advanced by in vivo imaging research. Arterial remodeling describes the expansion of a vessel at the site of accumulating plaque, delaying luminal stenosis. Despite minimal luminal stenosis, some of these lesions undergo sudden changes, plaque rupture, and intraluminal thrombosis. This is associated with acute coronary syndromes or, more frequently, asymptomatic plaque progression.

In summary, atherosclerosis is a systemic disease process, which manifests in a discontinuous and pulsatile manner, unpredictable in location and time. These characteristics of progression have implications for clinical atherosclerosis imaging, which has the goal of predicting the risk of future clinical events. Based on the systemic nature, it is unlikely that the observation of an individual lesion site will be sufficient. An optimal test would assess overall plaque burden and disease activity. This is reflected in the design of recent clinical studies of IVUS that use volumetric assessment of plaque burden in entire vessel segments as the primary end point and have demonstrated a relationship to markers of lipid metabolism and inflammation.<sup>2</sup> These trials and similarly designed studies with clinical end points support the use of atherosclerotic plaque burden as a surrogate end point.<sup>3</sup>

However, as Dr. Angelini points out, these surrogate end points will need to be validated in large studies with direct comparison to end points of morbidity and mortality. In the meantime, most experts



agree that atherosclerosis imaging with a wide range of invasive and noninvasive imaging modalities will have an increasing impact on clinical decision-making.<sup>4</sup>

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